Nitrimines as Reagents for the Metal-Free Construction of Carbon-Carbon and Carbon-Fluorine Bonds

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ABSTRACT

In the synthesis of increasingly complex molecules, many different tools are being employed to create difficult to access bonds. Transition-metal catalysis is one of the more widely studied and used methods, but there are drawbacks such as cost and toxicity that have called for greener alternatives. Investigations into the use of a relatively unstudied class of compounds called nitrimines has revealed potential for their employment in generating moieties with limited accessibility. Because of the previous success of using nitrimines to create carbon-nitrogen bonds, they are being investigated as a new family of reagents in the sustainable construction of carbon-carbon and carbon-fluorine bonds. The success of the carbon-carbon coupling reactions using nitrimines can be seen in the broad scope of the reaction as well as the *E/Z* selectivity control and application to the synthesis of a small target molecule. In addition, recent findings have shown promise with nitrimine use in creating vinyl fluorides and trifluoromethyl groups.

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1. INTRODUCTION

I. Transition Metal Free Chemistry

Many different methods have been developed in an effort to access new structures and synthesize increasingly complex molecules for their use in agrochemistry, pharmaceuticals, and materials. These methods vary widely in techniques used, but the most prevalent methods include the use of transition metals. While organometallic chemistry and transition-metal catalysis have provided a wealth of reactions and methods to achieve the desired products, there are inherent drawbacks to these methods that require consideration. Transition metals are typically expensive, and their ligands can not only be difficult to prepare but also very expensive in their own right.[1,3] In addition, co-catalysts or other additives are often necessary to promote the reactions leading to many very specific requirements in order to achieve the desired result.[2,3] The toxicity of these metal reagents also poses a problem. These methods are prominent in the area of pharmaceuticals, and many issues have arisen in the removal of such catalysts. There are strict guidelines limiting the amount of metals like palladium that can be present in the product after purification attempts,[4] yet the removal techniques still struggle on efficient ways to do this.[3] Separation is difficult to achieve and is often energy intensive and waste-generating.[5] Moreover, there are almost no methods of separation that recover these catalysts for future use, which further increases the cost and waste produced.[5] This leads to the environmental considerations of using such materials. As awareness and concern for environmental and sustainability issues grows, the issues with current organometallic chemistry become apparent. The rarity of many of the metals used indicates the unsustainability, and the toxicity is not environmentally friendly.[3,6] While

transition-metal catalysis and organometallic chemistry has allowed access to many different bond formations that are difficult to form synthetically and widely expanded the range of reactions at a chemist's disposal, the inherent drawbacks of their use suggests research into other methods is not only desirable but necessary.

One alternative that chemists have developed is through biocatalysis. This involves using enzymes as catalysts, which, because they are made from renewable raw materials, are biodegradable.[6] They also give high selectivity, require milder conditions, and often avoid the need for protecting groups.[6] While biocatalysis is certainly a respectable alternative, with numerous commercial processes taking advantage of it,[7] there are some shortcomings to it as well. Narrow substrate range, high costs, and solubility issues as well as costly and wasteful workup and purification steps[8] all inhibit biocatalysis from being the ideal green alternative to transition metal chemistry.

In recent years, another alternative has been discovered, or rather rediscovered, that of organocatalysis. In the 1800's and early 1900's there are scattered reports of using small organic molecules to catalyze reactions, from Liebig's use of acetaldehyde to Bredig's alkaloid-catalyzed cyanohydrin.[9,10] Fairly simple organic molecules can be very effective in their ability to catalyze reactions, even enantioselectively, to give "greener" versions of reactions that normally require transition metals.[9] There are a number of different classes of organocatalysts that have been developed. Enamine catalysis involves using a chiral secondary amine (a common example is L-proline) with a carbonyl in the reversible creation of an enamine in order to lower the LUMO and achieve the desired product enantioselectively.[11] Another example of organocatalysis involves the use of N-heterocyclic carbenes. Using carbenes derived from salts like

thiazolium or imidazolium, chemists have found numerous applications for catalysis, especially asymmetricly.[12] In the past ten years a new class of organocatalysis has emerged, that of hydrogen-bond donors involving the activation of an electrophile.[13] However, this field of catalysis is comparably very young and more research is necessary in order to broaden the scope of applicable reactions and to solve problems such as high catalyst loading and longer reaction times.

While organocatalysis shows promising applications, one might even go a step further and try to eliminate the need for catalysts altogether. If suitable activated reagents could be created with the ability to efficiently construct difficult moieties without a catalyst under mild conditions, then a third alternative could be considered. Here the issue comes in finding a reagent that is simple and inexpensive to create while still having an increased reactivity.

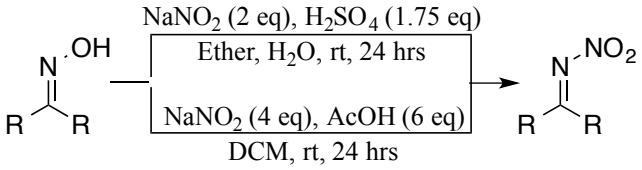
II. Nitrimines

Nitrimines are an underdeveloped class of compounds with scattered reports of unique reactivity. One of the earliest reports of these compounds was in 1895 by Angeli and co-workers, who synthesized what they called "pernitroso" compounds but were unable to definitively determine the structure.[14] Scholl was able to correctly propose the nitrimine structure later that year,[15] but for the next few years the limited reports dealing with nitrimines were still debating their true nature. The appearance of nitrimines in the literature dropped off until the mid-1900s, when there were infrequent reports of their use in specific reactions. One of the first was the ability to create hydrazones; combining furfuralnitrimine with phenylhydrazine gave 35% yield.[16] There are also a few papers describing the reduction of nitrimines to N-nitroamines with yields above 70%.[17] In

1979, Büchi and Wüest were able to transform different nitrimines into alkynes and allenes in yields as high as 76%.[18] Guziec and Russo used nitrimines as a way to access sterically hindered imines in very high yields with ammonia gas.[19] Nitrimines were shown to participate in a reaction to create N-heterocyclic compounds with a palladium catalyst in 87% yield.[20] They were also able to give 60% yield in a Knoevenagel Condensation with malononitrile.[21] In the 1990's, the Bondavalli group did multiple reactions with nitrimines including α-brominations and limited enamine synthesis in decently high yields.[22]

There are numerous ways chemists have designed to synthesize nitrimines. Suggitt and co-workers were able to achieve 42% yield with a condensation of 2-furaldehyde and nitroamine.[16] Steroidal alkenes will react with NOF to give α-fluorinated nitrimines.[23] Nitration of the imine was achieved through the addition of nitric acid and ammonium chloride in 77% yield.[24] However, it is common to prepare the oxime of the desired carbonyl and then create the nitrimine. Fuming nitric acid added to oximes gave various nitrimines in low yields.[25] Gaseous nitrosyl chloride can be used as well to give yields around 69%.[26]

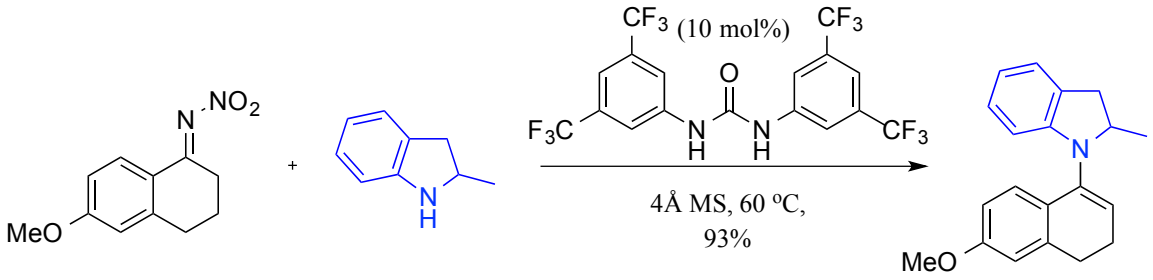
Scheme 1.1 Synthesis of Nitrimines



We currently employ two methods in our lab (Scheme1.1). The first involves dissolving the nitrimine in ether and combining that in a separatory funnel with sodium nitrite dissolved in water and then adding sulfuric acid dropwise.[27] The other involves reacting the nitrimine, sodium nitrite and acetic acid in DCM.[28]

Recently, we have proven the utility of nitrimines in creating sterically hindered enamines. Organometallic methods to prepare enamines as alternatives to more conventional methods (using Lewis or Brønsted acids) have been successful but still are limited by low functional group tolerance and the continued failure with hindered substrates.[29] Nitrimines were able to prove their value in the construction of carbon-nitrogen bonds in mild, reliable conditions. The nitro group is known to coordinate with hydrogen bond donor catalysts,[30] and the nitrimine has been used in a limited scope of enamine formations.[22b] Through their interaction with a hydrogen bond donor urea catalyst, the nitrimines were activated to allow for the direct formation of sterically hindered enamines under mild conditions (Scheme 1.2). This method was proven superior to the palladium-catalyzed conditions by giving good to high yields of products derived from sterically bulky reagents in which the palladium-catalyzed conditions were unable to generate. A large scope of both hindered nitrimines and secondary amines was tested and the urea activation of nitrimines was successful in all attempts.[31] The success in the C-N cross-coupling reactions suggested to us that nitrimine based methods had the potential for a broader scope of metal-free reactions.

Scheme 1.2 Nitrimines in the creation of sterically hindered enamines



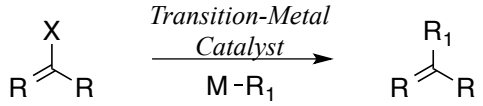
III. Carbon-Carbon Background

Cross-coupling reactions to create carbon-carbon bonds are remarkable tools for the dependable and effective synthesis of functional target molecules.[32] There are a wide variety of methods to catalyze coupling reactions with transition metal catalysts being considered some of the most reliable and effective tools to do so.[2] There has also been some recent work with metal free carbon-carbon cross-coupling reactions. In 2011, Yong and coworkers were able to do biaryl couplings using a stable zwiterionic radical catalyst to activate aromatic C-H bonds.[33] A year later, another method creating aryl carbon-carbon bonds to synthesize substituted phenanthridinones and dibenzoazepinones through a catalytic amount of 1,10-phenanthroline or AIBN in the presence of KO^{t}Bu was developed.[34] Another common carbon-carbon bond formation is α-alkylations and arylations of carbonyls. For example, in 2008 it was reported that DDQ could be used to promote the formation of carbon-carbon bonds between dicarbonyl compounds and diarylallyic compounds.[35]

While there are numerous types of carbon-carbon bonds to synthesize, we were most interested in the creation of di- and tri-substituted alkenes. A typical transition metal approach (Scheme 1.3a) uses vinyl or aryl halides, triflates, or mesylates as starting materials with the metal catalyst undergoing oxidative addition into the carbon halide/pseudohalide bond. Some specific examples of metal-catalyzed C(sp^2)-C(sp^2)

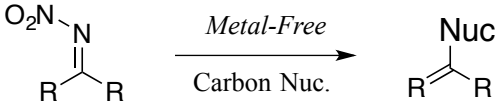
Scheme 1.3 Approaches to synthesize C(sp^2)-C(sp^2) bonds

a)

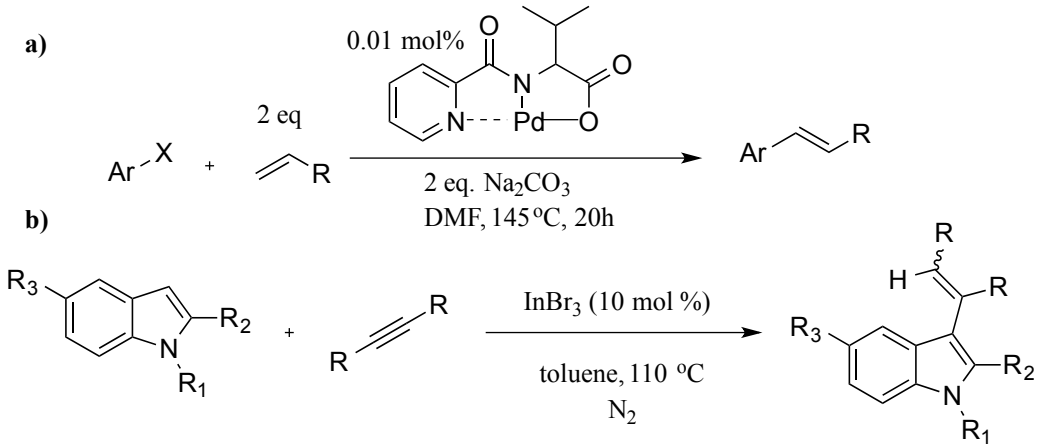


X = Cl, Br, I, OTf, OMs

b)



Scheme 1.4 Metal-catalyzed formations of $C(sp^2)$-$C(sp^2)$ bonds



cross-coupling reactions are shown in Scheme 1.4. Due to the drawbacks of using transition metals, we set out to develop a method to assemble useful $C(sp^2)$-$C(sp^2)$ bonds without that requirement. Unlike the other transition metal-free cross-coupling methods mentioned above, the prevalence of methods to achieve this type of bond is much less. To this end, we believed that nitrimines could serve as a highly activated replacement to carbonyls and react with a carbon nucleophile to produce a substituted alkene (Scheme 1.3b). Examples of biologically active molecules that served as inspiration in determining

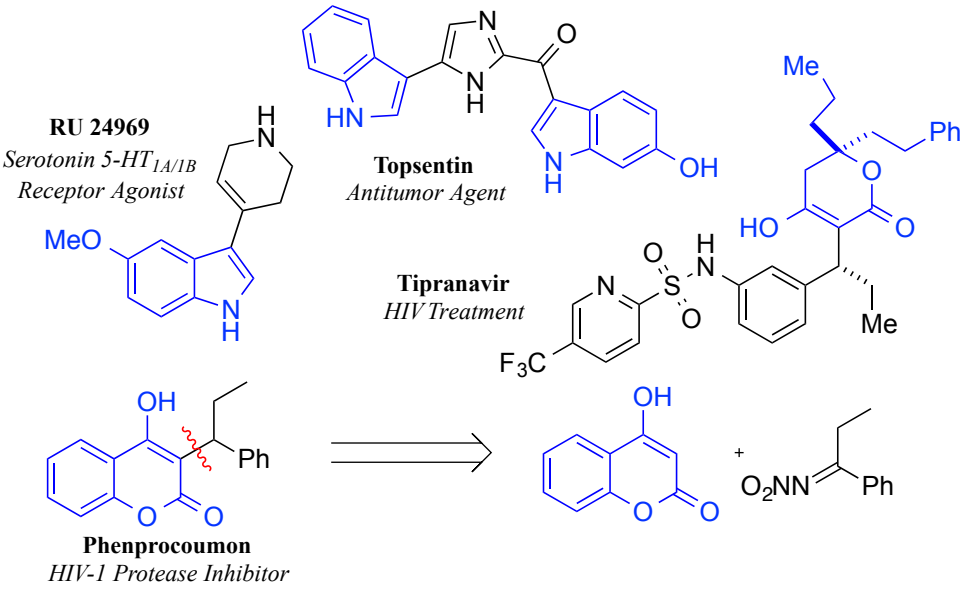


Figure 1.1 Examples of molecules that could potentially be synthesized by nitrimines

useful methods are shown in Figure 1.1. The retrosynthesis of phenprocoumon with a nitrimine starting material shows how this method could conceivably be applied to a small target molecule.[37]

IV. Carbon-Fluorine/Trifluormethyl Background

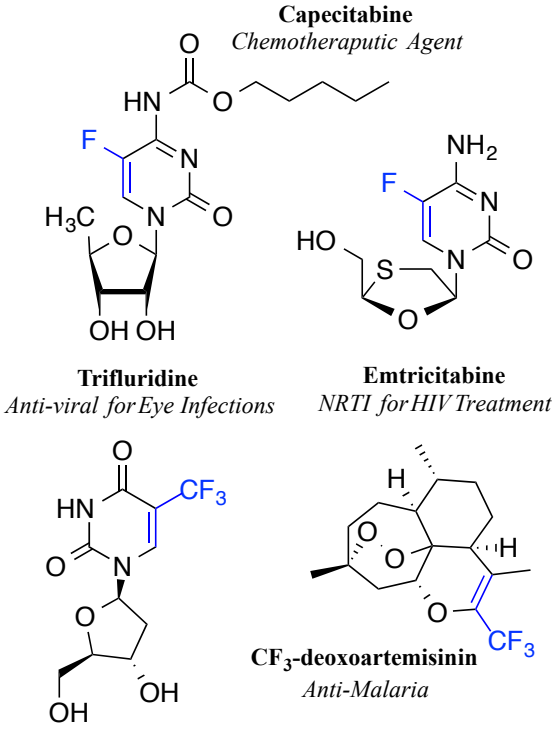
The reactivity of nitrimines suggested to us that a wide range of nucleophiles had the potential to react with them. To this end, we began to consider other nucleophilic sources that could add to nitrimines towards the creation of challenging bonds. In recent years, fluorine has become very prevalent in a lot of pharmaceuticals. In 2012, 20 of the top 100 drugs sold in America contained at least one fluoride or trifluoromethyl group.[38] Their frequency in these molecules comes from the improved bioavailability and binding affinity to certain receptors in the body.[39] Finding ways to incorporate fluorine into molecules has become increasingly popular and necessary in many fields including medicinal chemistry and agrochemistry as well as techniques like ^{18}F positron emission tomography (PET).

Traditionally, fluorine chemistry has involved the use of harsh reaction conditions and undesirable reagents like F_2 and HF. As fluorination chemistry increased in importance, new fluorination reagents (both electrophilic and nucleophilic) as well as transition-metal catalysis have allowed more selective and less severe methods to be developed. Numerous methods to achieve aromatic fluorinations have been designed, usually employing a metal catalyst like silver, copper, or palladium. Allylic fluorinations have been done with iridium and palladium, and alkyl fluorinations can involve cobalt or iron catalysts. Most of the fluorination work done without metals involves fluorination of the α position of a carbonyl.[40]

Another way to incorporate fluorine into molecules is through the use of a trifluoromethyl group. Hypervalent iodine reagents in conjunction with metal catalysts have been identified as one way to trifluoromethylate aromatics, carbonyls, and allylic positions.[41] There are also many examples of using copper to catalyze trifluoromethylation reactions additions in numerous systems using sulfur based reagents.[42] Chiral ammonium salts have been used to asymmetrically trifluoromethylate carbonyls to tertiary alcohols both with metal based catalysts and without.[43]

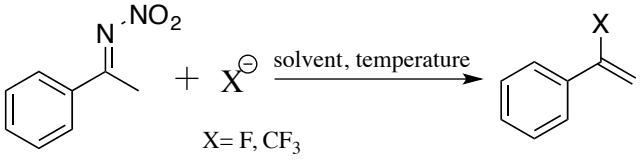
Of particular interest to us was nucleophillic fluorinations and trifluoromethylations, predominantly in the creation of vinyl fluorides and trifluoromethyl groups. A fluorine presence on an alkene causes the moiety to mimic the dipole nature of amides, making vinyl fluorides suitable bioisosteres of amide bonds.[44] Scientists will replace the amid bond of a molecule or enzyme with a vinyl fluoride and observe the bioactivity in order to asses the importance of the chemical structure of a molecule or enzyme.[45] Trifluoromethyl groups have superior metabolic stability and increased lipophilicity compared to methyl analogs.[42] Examples of vinyl fluorides and trifluoromethyl groups on biologically active molecules are shown in Figure 1.2.

Figure 1.2 Examples of Pharmaceuticals with vinyl fluorides and Trifluoromethyl groups



While these bond formations have proven to be more difficult, there have been a few methods reported. Using a gold catalyst, Sadighi and co-workers were able to selectively add HF across alkynes to afford the vinyl fluoride.[46] In addition there are a few examples of cross-coupling α-fluorinated benzothiazol sulfone based sythons with carbonyls and enones to create vinyl fluorides.[47] One of the most prevalent methods to obtain vinyl fluorides is through elimination reactions after the installation of fluorine.[48] A greater part of previous examples to synthesize vinyl trifluoromethyl compounds involve the use of metals. Cho and Buchwald were able to synthesize vinyl trifluoromethyl groups from vinyl sulfonates with a palladium based catalyst.[49] A few copper mediated vinyl trifluoromethylation methods have also been developed.[42] An iodotrifluoromethylation of alkynes was also developed without the need for metal catalysis.[50]

Scheme 1.5 Proposed nitrimine-based method



We believe that the application of nitrimines to this matter will provide a suitable alternative giving a more direct access to both vinyl fluorides and trifluoromethyl groups as seen in Scheme 1.5.

D. RESULTS

I. Carbon-Carbon Cross-Coupling[37]

Initially, conditions for carbon-carbon bond formations were developed using the nitrimine derived from 6-methoxytetralone and 2-methylindole. Two different sets of reaction conditions were optimized to yield the cross-coupled product (Scheme 2.1). Conditions A employed 20 mol % of Schreiner's urea (1,3-bis[3,5-bis(trifluoromethyl)phenyl] urea)[51] to catalyze the reaction in toluene at 50 °C for 24 hourrs to give modest yields of the coupled product. It was found that an additive hexafluoroisoproanol (HFIP) in neat conditions yielded 32% of the product. Thus, conditions B were optimized (Table

Scheme 2.1 Reaction conditions for $C(sp^2)$-$C(sp^2)$ coupling

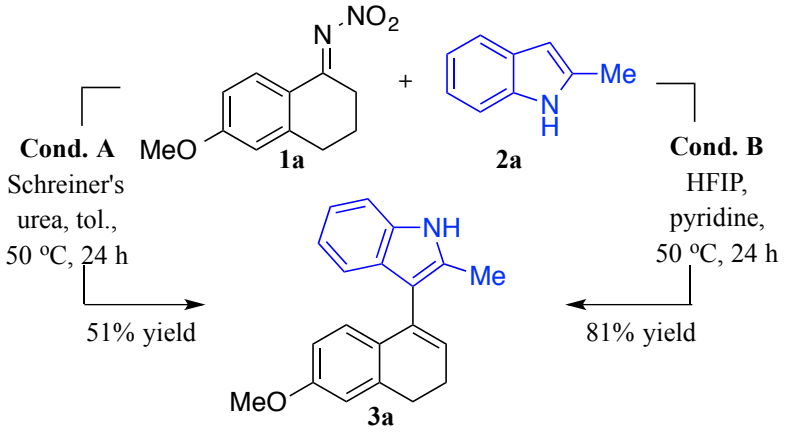
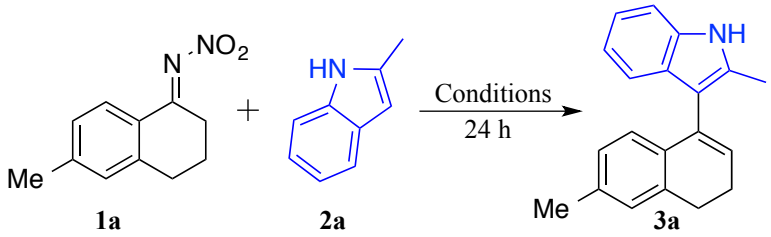


Table 2.1 Optimization of Conditions B



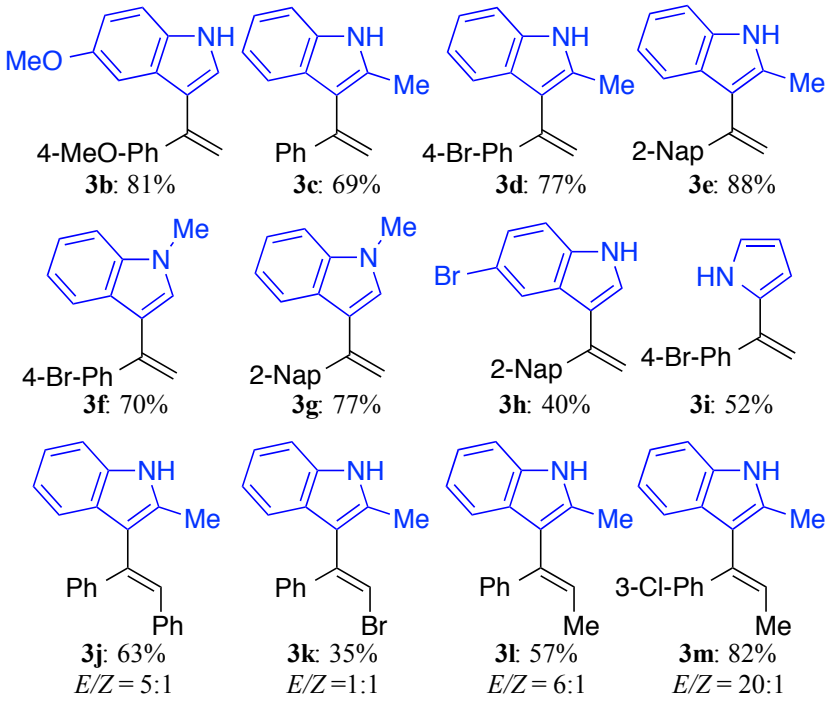
2a (equiv)	Solvent	Base	Temp. (°C)	Additive	Yield* (%)
4	DMSO	pyridine	50	HFIP (2 eq)	0
4	DMF	pyridine	50	HFIP (2 eq)	0
4	*i*PrOH	pyridine	60	HFIP (2 eq)	7
2	toluene	pyridine	70	HFIP (2 eq)	15
2	neat	pyridine	70	HFIP (2 eq)	32
2	neat	pyridine	70	TFE (2 eq)	21
4	neat	pyridine	70	None	8
2	neat	pyridine	70	HFIP (5 eq)	61
4	neat	DMAP	70	HFIP (5 eq)	30
4	neat	DTBMP	70	HFIP (5 eq)	68
4	neat	pyridine	70	HFIP (5 eq)	71
4	neat	pyridine	23	None	0
4	neat	pyridine	50	HFIP (20 eq)	81

*Reported Yields determined by ^{1}HNMR

2.1) and it was determined that no catalyst was necessary, HFIP as solvent, and pyridine gave high yields after 24 hours at 50 °C.

With the use of less sterically bulky nitrimines, however, the necessity of HFIP decreased. The HFIP actually facilitated di-addition of the carbon-nucleophile, and it was found that removing the HFIP completely and running the reaction neat resulted in yields that were still satisfactory. After confirming conditions for the cross-coupling reaction, we expanded the nitrimines and carbon nucleophiles tested in a substrate scope (Figure 2.1). The 2-methylindole was able to add to a variety of nitrimines, both electron rich and electron poor.

Figure 2.1 Substrate scope of cross-coupling reaction



The reaction was tolerant of a variety of indole derivatives, even *N*-methylindole. It should be noted, however, that adding *N*-methylindole worked better under conditions A with Schreiner's urea. Other carbon nucleophiles like pyrrole were also able to couple to the nitrimine. When the reaction was carried out with the corresponding parent ketones of the nitrimines, no product was observed, meaning the nitrimine is necessary for this reaction to proceed.

Furthermore, not only were we able to synthesize terminal di-substituted alkenes, but we were also able to access some sterically hindered tri-substituted alkenes. The deoxybenzoin nitrimine yielded **3k** in 63% with a 5:1 ratio of *E/Z* isomers. The vinyl bromide product, **3k**, presented less selectivity. The propiophenone nitrimine gave **3l** in 57% yield and a 6:1 mixture of *E/Z*. The best diastereocontrol over alkene geometry was **3m**, having a 20:1 ratio of *E/Z* in high yield. We were able to adjust and monitor the reaction conditions (Scheme 2.2) in order to exert control over the final geometry of the double bond. Conditions A favored the *E* geometry. By lowering the temperature and equivalents of indole the *Z* alkene was favored.

Scheme 2.2 Conditions to control alkene geometry

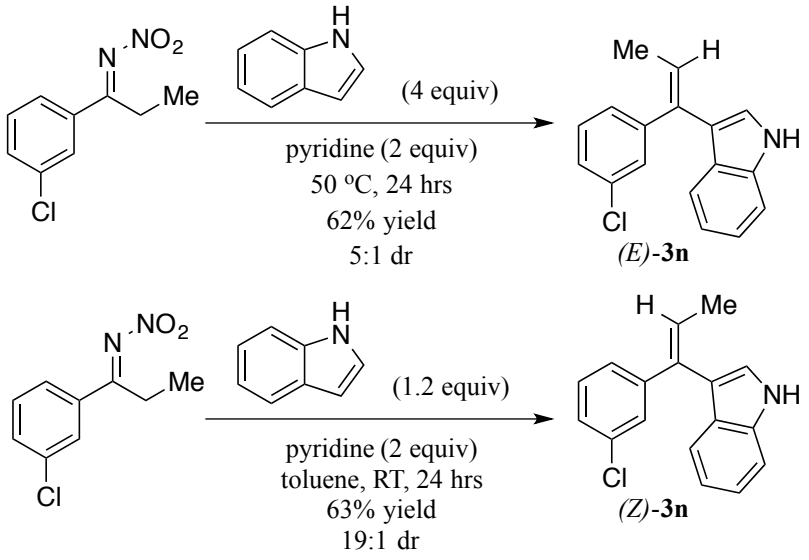
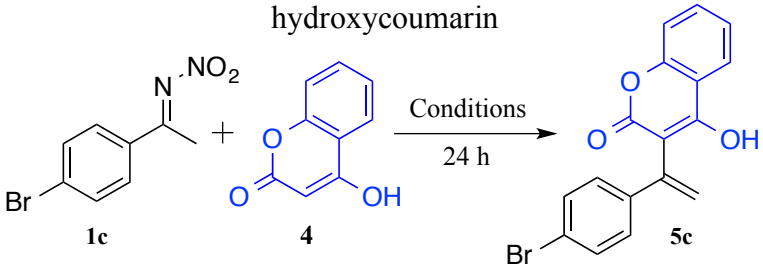


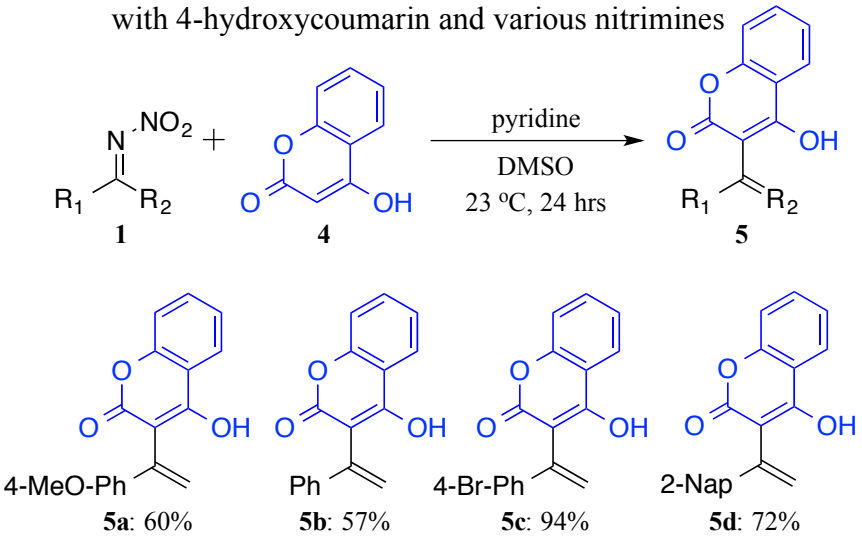
Table 2.2 Optimization of coupling with 4-hydroxycoumarin



4 (equiv)	Solvent	Temp. (°C)	Pyridine (equiv)	Yield* (%)
4	none	50	2	35
4	toluene (0.5 M)	50	2	0
4	toluene (0.5 M)	60	2	0
4	DMSO (1 M)	23	2	84
4	toluene (1 M)	23	2	10
4	DMSO (1 M)	23	0	80
4	DMSO (1 M)	23	1	91
2	DMSO (1 M)	23	1	94
2	DMSO (2 M)	23	1	88
2	DMSO (0.5 M)	23	1	92

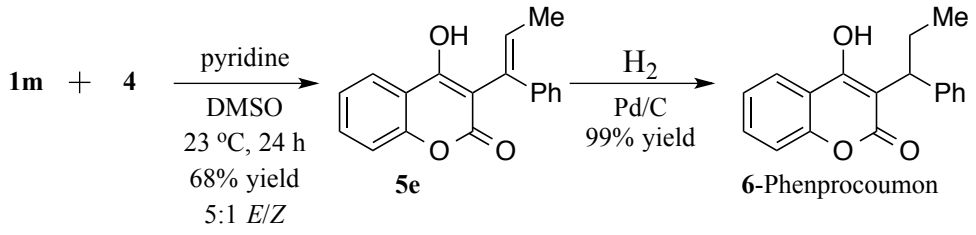
*Reported Yields determined by ^{1}HNMR

Scheme 2.3 Selected examples of cross-coupling reaction with 4-hydroxycoumarin and various nitrimines

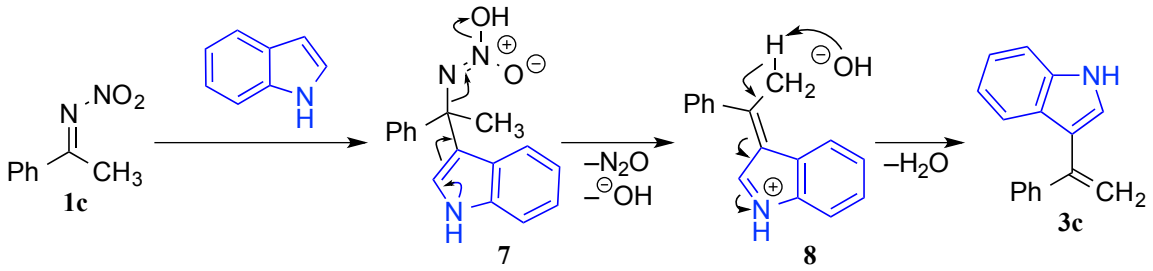


The success of the cross-coupling reaction with nitrogen-based heterocycles prompted us to try other carbon nucleophiles in an attempt to synthesize a small target molecule. With nitrimine **1c** and 4-hydroxycoumarin, the conditions were reoptimized (Table 2.2). With a modification of the reaction conditions (DMSO as solvent), we were able to add hydroxy-coumarins to a variety of nitrimines in high yields (Scheme 2.3). Again, it was found that when the reaction was carried out with the corresponding parent ketones of the nitrimines, no product was observed. Pleased that numerous nitrimines were able to couple with 4-hydroxycoumarin, we attempted the synthesis of phenprocoumon by coupling the propiophenone nitrimine and 4-hydroxycoumarin (Scheme 2.4). The desired trisubstituted alkene was achieved in 68% yield as a 5:1 mixture of *E*:*Z* isomers. The double bond was then hydrogenated in quantitative yield through standard reaction conditions to afford the desired product.

Scheme 2.4 Synthesis of phenprocoumon employing the nitrimine based cross-coupling reaction



Scheme 2.5 Proposed reaction pathway for C(sp^2)–C(sp^2) cross- coupling reactions



The proposed reaction pathway of the C(sp^2)-C(sp^2) cross-coupling reactions is shown in Scheme 2.5. It is believed that the nucleophile (e.g. indole) attacks the carbon of the nitrimine in a Friedel-Crafts like manner which is then followed by rearomatization to give **7.** The loss of nitrous oxide and hydroxide gives rise to the imminium ion, **8**, which then undergoes deprotonation to yield the product **3c** and water.

There is some evidence to support this mechanism. The evolution of nitrous oxide with an addition to a nitrimine has been observed before.[16] In addition, when molecular sieves are removed from the reaction vial, a prominent amount of the ketone hydrolysis product is observed suggesting that water is being made. Both of these molecules are generated in the proposed pathway. To further study the mechanism, a Hammett Plot analysis was performed. Using acetophenone as the control, electron

X Substituent	Log (X yield/H yield)	σ_p-Value
H	0	0
4-MeO	-0.41218	-0.27
4-Me	-0.12963	-0.14
4-F	0.36597	0.15
4-Br	0.50864	0.26
4-CF_3	0.62258	0.53

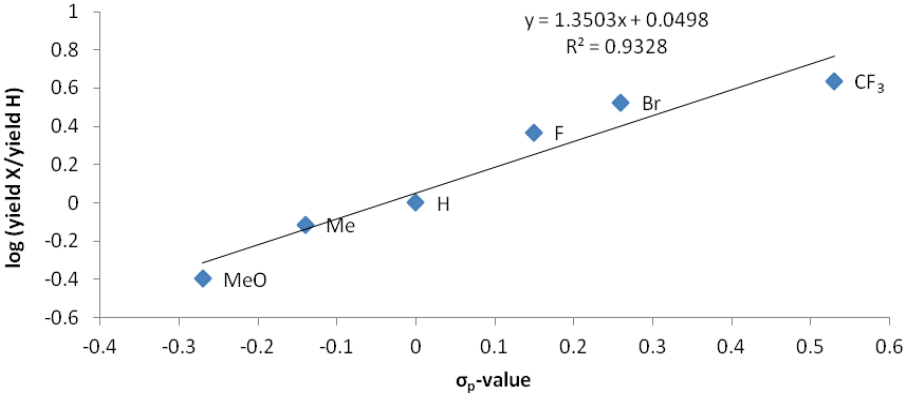


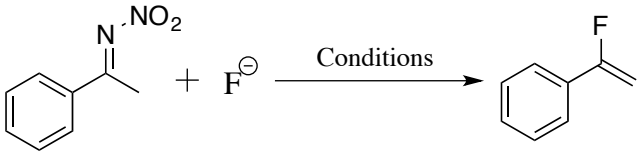
Figure 2.2 Hammett Plot for nitrimine cross coupling reaction with indole

donating and withdrawing substituted acetophenones were reacted with indole under conditions B without the HFIP. After one hour, 10 μL aliquots of each reaction retrieved and diluted in 0.6 mL of $CDCl_3$ for quantitative ^1H NMR analysis using ferrocene as an internal standard. A Hammett Plot was then constructed as seen in Figure 2.2. The positive slope of $\rho = 1.35$ suggests that the transition state of the rate determining step of the mechanism involves either the development of a negative charge (as in the addition of the nucleophile to the nitrimine) or the disappearance of a positive charge (as in the deprotonation of the vinylic methane). While it does not prove the pathway is correct, this evidence does support the proposed mechanism.

II. Carbon-Fluorine Bond Formations

Unlike the carbon nucleophiles above, the smaller fluoride ion is a much more concentrated negative charge. The acetophenone nitrimine was chosen for optimization as the vinyl fluoride product is known in the literature and those reports could be used for verification.[52] There are many different sources of nucleophilic fluoride each with its own benefits and drawbacks, and the first challenge in creating these carbon-fluorine bonds is determining which source with which conditions adds the most efficiently onto the nitrimine compounds. Presented below are the different sources of fluoride attempted and the difficulties faced with each. One of the most well known sources of nucleophillic fluoride is potassium fluoride. Many different combinations of reaction conditions were attempted with KF (2 equiv), as can be seen in Table 2.3. Toluene was the first solvent chosen because the nucleophilicity of the fluoride ion decreases in polar solvents due to its strong hydrogen-bonding nature.[53] However, this makes it a stronger base as well. In addition, it is difficult to dissolve in non-polar solvents due to the high lattice energy of

Table 2.3 Reaction conditions to create vinyl fluorides with potassium fluoride



18-Crown-6 (equiv)	Pyridine (equiv)	Schreiner's Urea (equiv)	Solvent	Temp. (°C)	Time (hrs)	Result
2	-	-	Tol. (1 M)	23	24	nitroenamine
2	2	0.2	Tol. (1 M)	23	24	nitroenamine
2	2	-	Tol. (1 M)	23	24	nitroenamine
2	-	0.2	Tol. (1 M)	23	24	nitroenamine
1	2	-	MeOH (1 M)	23	24	side product
1	2	0.2	MeOH (1 M)	23	24	side product
0	-	-	MeOH (1 M)	23	24	nitroenamine
1	-	-	MeOH (1 M)	23	24	nitroenamine
2	-	-	MeOH (1 M)	23	24	nitroenamine
1	-	-	Tol. (1 M)	40	24	nitroenamine
1	-	-	Tol. (1 M)	40	24	nitroenamine
1	2	-	Tol. (1 M)	40	24	nitroenamine
1	2	0.2	Tol. (1 M)	40	24	nitroenamine
2	2	-	CH3CN (1M)	80	24	ketone
2	2	-	CH3CN (1M)	80	24	ketone
0.25	-	-	Tol. (1 M)	60	24	nitroenamine
0.5	-	-	Tol. (1 M)	60	24	nitroenamine
1	-	-	Tol. (1 M)	60	24	nitroenamine
2	-	-	Tol. (1 M)	60	24	nitroenamine
1	-	-	Tol. (0.5 M)	60	24	side product
1	-	-	Tol. (0.25 M)	60	24	side product
1	-	-	Tol. (1 M)	23	2	nitroenamine
1	-	-	Tol. (1 M)	40	2	nitroenamine
0.5	-	-	Tol. (1 M)	0	0	no rxn

fluoride salts.[40] The additive of 18-crown-6 ether is commonly used to help the solubility of KF. It was also thought that the 18-crown-6 would sequester the potassium and free up the fluoride in order to attack the nitrimine. Pyridine was also tested in these reactions based on our previous work with nitrimines. We propose that the pyridine may facilitate in the deprotonation step of the proposed pathway. In addition, the nitrimine coordination with a urea catalyst is known, and so Schreiner's urea was tested as well. A mixture of results was obtained. Frequently, a doublet with peaks around 5.2 ppm and 5.12 ppm was observed in the ^{1}H NMR spectra. After some consideration, it was determined that these peaks most likely corresponded to the nitroenamine form of the

nitrimine. The fluoride ion was most likely acting as a base and abstracting an alpha hydrogen instead of attacking the nitrimine, leading to the formation of the nitroenamine. In addition, numerous side products were observed in the ^{1}H NMR spectra between 5.3 – 7 ppm. After a few attempts, one side product was isolated, and a few characteristic studies (mass spectrometry, ^{13}C NMR, and ^{19}FNMR spectroscopy) were performed. It is believed that the side products are a combination of two nitrimine or nitroenamine molecules with the incorporation of at least one fluorine. The conditions were altered in many ways in order to try and favor nucleophilic attack over the formation of the nitroenamine and to prevent the nitrimine, nitroenamine, and the vinyl fluoride product from further reacting. The reactions were both diluted and cooled down to reduce side reactions with little success.

A different potassium fluoride source, KHF_2, was also attempted. Four equivalents of KHF_2 with four equivalents of 18-crown-6 without pyridine, with pyridine, and with pyridine and Schreiner's urea were run at 50 °C for 24 hours. Only the reaction with the urea catalyst showed any new ^{1}HNMR peaks, and these did not correspond to the product.

Table 2.4 Reaction conditions to create vinyl fluorides with cesium fluoride

15-Crown-5 (equiv)	Pyridine (equiv)	Schreiner's Urea (equiv)	Solvent	Result
2	-	-	Tol. (1 M)	nitroenamine/side product
2	2	0.2	Tol. (1 M)	nitroenamine/side product
2	2	-	Tol. (1 M)	nitroenamine/side product
2	-	0.2	Tol. (1 M)	nitroenamine/side product
1	2	-	MeOH (1 M)	nitroenamine
1	2	0.2	MeOH (1 M)	nitroenamine
0	-	-	MeOH (1 M)	nitroenamine
1	-	-	MeOH (1 M)	nitroenamine
2	-	-	MeOH (1 M)	nitroenamine

The next fluoride source to be tested was cesium fluoride (Table 2.4). The issues to overcome with

cesium fluoride closely mirror those of potassium fluoride. The 15-crown-5 was used in a similar purpose to help with the solubility of the salt and the trapping of the cesium ion. Doublets in the ^{1}H NMR spectrum around the same 5.2 – 5.1 ppm range we attributed to the nitroenamine, and other side products between 5.3 – 7 ppm range were also observed.

A few trials with silver fluoride were also carried out. Two equivalents of AgF in toluene (1 M) at both room temperature and 40 °C was reacted for 24 hours. No product or side products were observed, there was only recovered nitrimine.

Another common fluoride source is tetrabutylammonium fluoride (TBAF). The trials conducted with TBAF-THF are shown in Table 2.5. In conjunction with TBAF, tBuOH is often added.[40] The results closely mirror that of the potassium fluoride. The common product of these reactions showed up in the ^{1}H NMR spectrum as a doublet at around 5.25 ppm and 5.10 ppm. These peaks while slightly different from that of fluoride sources already mentioned, were still attributed to the nitroename, the small shifts probably due to solvent effects.

Table 2.5 Reaction conditions to create vinyl fluorides with TBAF

tBuOH	Time (hrs)	Result
-	24	nitroenamine
(0.5 M)	24	nitroenamine
-	3	nitroenamine
(0.5 M)	3	nitroenamine

Similar to TBAF is tetramethylammonium fluoride (TMAF). This source of fluorine is sometimes considered less basic than TBAF because it cannot undergo the Hoffman Elimination. A solvent screen with 2 equivalents of TMAF was conducted at room temperature for two hours resulting in ^{1}HNMR peaks between the range of 5.1-5.3 ppm, none of which corresponded to the desired product.

Finally, diethylamminosulfur trifluoride (DAST) was tried (Table 2.6). DAST was developed as a milder sulfur-based fluorinating reagent (compared to SF_4). It

operates under fairly mild conditions to convert hydroxyl and carbonyl oxygens to fluorine; however, it is also unstable in higher temperatures and can detonate.[42] DCM is a very common solvent to see with DAST[42] and was used for these trials. After concentrating and heating up the reaction did not lead to any reaction, we took a closer look at the mechanism of DAST. Usually the first step is displacement of a fluoride from the sulfur atom by attack of an oxygen from the hydroxyl or carbonyl compound. We believed that an oxygen from the nitrimine was not completing this step, and so a hindered alcohol was added in order initiate the reaction. While a reaction did take place, the desired product was not observed.

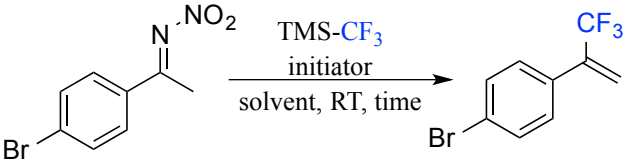
Table 2.6 Reaction conditions to create vinyl fluorides with DAST

DAST (equiv)	tBuOH (equiv)	DCM	Temp. (°C)	Time (hrs)	Result
5	-	0.275 M	23	24	no rxn
5	-	0.275 M	23	24	no rxn
5	-	1 M	23	24	no rxn
5	-	1 M	23	24	no rxn
5	-	1 M	35	24	no rxn
5	-	1 M	35	24	no rxn
1.5	1.5	2M	23	3	side product
3	3	2M	23	3	side product

III. Trifluormethylations

To first test and optimize the trifluoromethylation reactions, the 4'-bromoacetophenone nitrimine was chosen, as the vinyl trifluoromethyl product has been reported in the literature and could be used for verification.[54] The source of the CF_3 anion selected was Ruppert's Reagent (TMS-CF_3). Developed in

Table 2.7 Optimization of vinyl trifluoromehtylation reaction



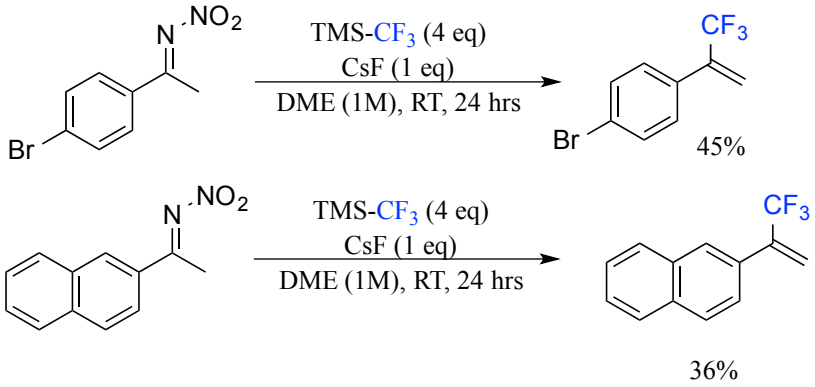
Initiator	Equiv of TMS-CF_3	Solvent	Time (hrs)	Yield*
KF (2 eq)	2	Dioxanes (0.3 M)	24	0%
KOH (6 eq)	2	Toluene (0.5 M)	24	0%
CsF (0.1 eq)	2	DME (0.5 M)	24	3%
CsF (0.5 eq)	2	DME (0.5 M)	24	11%
CsF (0.5 eq)	2	THF (0.5 M)	24	0%
CsF (1 eq)	2	DME (0.5 M)	24	10%
CsF (1 eq)	2	THF (0.5 M)	24	0%
CsF (1 eq)	1.5	DME (1 M)	48	17%
CsF (1 eq)	2	DME (1 M)	48	31%
CsF (1 eq)	3	DME (1 M)	48	34%
CsF (1 eq)	4	DME (1 M)	48	56%

*Reported Yields are ^{1}HNMR

1984 by Ingo Rupert, it is an easily prepared source for the CF_3 anion.[55] Prakash and coworkers were the first to use it to add CF_3 anion to a carbonyl compound.[56] Table 2.7 shows the optimization using Ruppert's Reagent with different initiators. It was found that cesium fluoride was the best initiator with DME as the solvent. Different equivalents of Ruppert's Reagent were then tested, with 4 equivalents giving the best yield.

Pleased that the reaction conditions were proving effective, we recently were successful in attempting to isolate the desired product in a 45% yield. In addition, these conditions were applied using the 2-naphthelene nitrimine, and again the product was able to be isolated in a 36% yield. While these results are promising, we are attempting further optimization. As the nature of the nitrimine gets less reactive, the conditions developed no longer are adequate to create the product, and further study is still being conducted.

Figure 2.3 Isolated vinyl trifluoromethyl products



E. CONCLUSIONS

The relatively unstudied class of nitrimine compounds has the potential to offer metal-free alternative methods to synthesize difficult to access bonds through their unique reactivity. Nitrimines were proven to couple with different carbon nucleophiles under mild conditions giving di- and tri-substituted alkenes in moderate to high yields. In addition, stereocontrol of the alkene geometry is possible through modifications of the initial conditions. The developed cross-coupling method was also shown to be useful in the synthesis of a small target molecule, phenprocoumon. Additional work in our laboratory is being conducted to show the utility of this method in the synthesis of a larger target molecule.

Other studies being conducted with nitrimines are showing promising results as well. While the vinyl fluorine product has not been observed, the numerous side products resulting from the different reactions suggest that fluorine is being incorporated. The basicity of the fluorine ion is a challenge to the reaction that we are working to suppress. However, with further optimization we believe that vinyl fluorides will be accessible with the use of nitrimines. In addition, the creation of the vinyl trifluoromethyl products has had promising beginnings, and with modifications to the conditions we believe other nitrimines can be reacted with Ruppert's Reagent and the vinyl trifluoromethyl products can be isolated in good yield.

Further studies in our laboratory are exploring other opportunities for nitrimines as reagents in metal-free chemical reactions, and we are excited to see where their potential leads us as our understanding of their reactivity grows.

F. SUPPORTING INFORMATION[37]

General Methods: Diethyl ether, tetrahydrofuran, dichloromethane, and toluene were purified by passage through a bed of activated alumina.[1] Purification of reaction products was carried out by flash chromatography using Sorbent Technologies 60 Å (40 - 63 μm). Analytical thin layer chromatography was performed on EMD Chemicals 0.25 mm silica gel 60-F254 plates. Visualization was accomplished with UV light and ceric ammonium molybdate stains followed by heating. Melting points (**mp**) were obtained on a Thermo Scientific Mel-temp apparatus and are uncorrected. Infrared spectra (**IR**) were obtained on a Perkin Elmer Spectrum 100R spectrophotometer. Infrared spectra for liquid products were obtained as a thin film on a NaCl disk, and spectra for solid products were collected by thin film deposition on an NaCl disk. Proton nuclear magnetic resonances (**^{1}H NMR**) were recorded in deuterated solvents on a Bruker Avance DPX 400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) using the solvent as internal standard ($CHCl_3$, δ 7.26). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br). Coupling constants are reported in Hertz (Hz). Proton-decoupled carbon (**^{13}C-NMR**) spectra were recorded on a Bruker Avance DPX 400 (100 MHz) spectrometer and are reported in ppm using the solvent as an internal standard ($CHCl_3$, δ 77.16). Electrospray mass spectra (**ESI-MS**) were obtained using a Bruker MicrOTOF Mass Spectrometer. Schreiner's urea catalyst was prepared according to Kotke and Schreiner's procedure.[57]

Procedures for the preparation of nitrimines 1a-1i:

CAUTION: It is well known that certain nitrimines are explosive. We observed no instability in the compounds reported in this paper; however, appropriate precautions should be taken when preparing and working with previously unknown nitrimine compounds.

General Procedure A

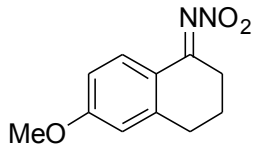
A flame-dried round bottom flask equipped with a stir bar and addition funnel was placed under positive N_2 pressure and charged with an oxime (6 mmol), dichloromethane (70 mL) and $NaNO_2$ (30 mmol) in that order. A solution of glacial acetic acid (10 mL) in DCM (30 mL) was added dropwise with stirring over one hour as gas evolved from the reaction. The reaction was allowed to stir for an additional hour and then filtered through a Celite plug to remove any precipitates. The filtrate was washed with water (50 mL) and $NaHCO_3$ (25 mL) and the organic layer was dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash column chromatography as detailed below to afford the pure nitrimine.

General Procedure B

A separatory funnel was charged with a solution of an oxime (80 mmol) in diethyl ether (140 mL) and then a saturated aqueous solution of $NaNO_2$ (195 mmol) was added in one portion. Sulfuric acid (80 mmol, 2 M) was added cautiously in small portions over 10 minutes as the separatory funnel was swirled vigorously and gas evolved. The reaction mixture was allowed to sit for an additional 15 minutes and then the aqueous layer was drained and the organic layer filtered through a plug of Celite to remove precipitates. The filtrate was extracted with water (100 mL x 2) and $NaHCO_3$ (50 mL), dried over Na_2SO_4

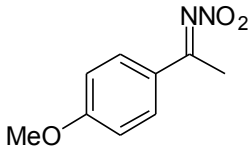
and concentrated. The crude mixture was purified by silica gel flash column chromatography as detailed below to afford the pure nitrimine.

Synthesis of 6-Methoxytetralone Nitrimine (1a):



To a solution of hydroxylamine hydrochloride (2.65 g, 38.2 mmol) and sodium acetate trihydrate (4.33 g, 31.8 mmol) in 30 mL water was added a solution of 6-methoxytetralone (4.49 g, 25.5 mmol) in 20 mL of methanol. The mixture was stirred for 12 hours at 60 °C. Next, the methanol was removed under reduced pressure to give a white slurry which was passed through a medium porosity ceramic filter, washing with water (3 x 10 mL), to give the oxime (4.85 g, 95%) as a white powder. The oxime (4.9 g, 25.5 mmol) was subjected to General Procedure B to give the crude nitrimine which was purified by flash column chromatography on silica gel (10:90 DCM/Hexanes to 50:50 DCM/hexanes) to give nitrimine **3a** as a pale yellow solid (2.22 g, 42%). R_f = 0.33 (50:50 DCM/hexanes); mp 107-109 ºC; IR (NaCl) 3055, 2981, 1609, 1580, 1556, 1423, 1261, 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.8 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.70 (d, *J* = 2.4 Hz, 1H), 3.86 (s, 3H), 2.92 (t, *J* = 6.2 Hz, 2H), 2.61 (t, *J* = 6.6 Hz, 2H), 2.12 (quin, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 163.8, 145.9, 128.8, 120.6, 113.9, 113.2, 55.6, 29.9, 27.8, 22.0; HRMS (ESI): Mass calculated for $C_{11}H_{12}N_2O_3$ $[M+Na]^+$, 243.0740. Found $[M+Na]^+$, 243.0729.

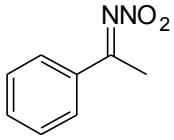
Synthesis of 4'-Methoxyacetophenone Nitrimine (1b):



To a solution of 4'-methoxyacetophenone (4.00 g, 26.6 mmol) in 30 mL of ethanol was added hydroxylamine hydrochloride (2.78 g, 40.0 mmol) and pyridine (3.23 mL, 40.0 mmol). The mixture was

stirred for 22 hours at 75 °C. Next, the ethanol was removed under reduced pressure to give a white slurry. The slurry was dissolved in diethyl ether (30 mL), washed with water (3 x 30 mL) and NaCl (30 mL), dried over Na_2SO_4, and concentrated to give the oxime (4.40 g, 99%) as a white solid. The oxime was subjected to General Procedure A to give the crude nitrimine which was purified by flash column chromatography on silica gel (100% Hexanes to 50:50 DCM/hexanes) to give nitrimine **2e** as a yellow solid (0.6573 g, 13%). R_f = 0.29 (30:70 DCM/hexanes); mp 46-49 ºC; IR (NaCl) 3013, 2936, 2840, 1599, 1563, 1462, 1284, 1258, 1177, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.1 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 163.7, 130.0, 125.3, 114.4, 55.8, 16.4; HRMS (ESI): Mass calculated for $C_9H_{10}N_2O_3$ $[M+Na]^+$, 217.0584. Found $[M+Na]^+$, 217.0592.

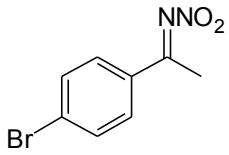
Synthesis of Acetophenone Nitrimine (2c):



To a solution of acetophenone (4.00 g, 33.29 mmol) in 35 mL of ethanol was added hydroxylamine hydrochloride (3.47 g, 49.9 mmol) and pyridine (4.04 mL, 49.9 mmol). The mixture was stirred for 6 hours at 60 °C. Next, the ethanol was removed under reduced pressure to give a white slurry. The slurry was dissolved in diethyl ether (30 mL), washed with water (3 x 30 mL) and NaCl (30 mL), dried over Na_2SO_4, and concentrated to give the oxime (4.47 g, 99%) as a white solid. The oxime was subjected to General Procedure A to give the crude nitrimine which was purified by flash column chromatography on silica gel (5:95 diethyl ether/hexanes) to give nitrimine **2d** as a white solid (0.6524 g, 12%). R_f = 0.15 (5:95 diethyl ether/hexanes); mp 56-59 ºC; IR (NaCl) 3058, 2931, 1604, 1563, 1283 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87−7.85 (m, 2H), 7.60−7.56 (m, 1H), 7.50−7.46 (m, 2H),

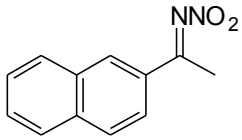
2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 133.2, 129.1, 128.0, 16.8; HRMS (ESI): Mass calculated for $C_8H_8N_2O_2Na$ $[M+Na]^+$, 187.0478. Found $[M+Na]^+$, 187.0486.

Synthesis of 4'-Bromoacetophenone Nitrimine (1d):



To a solution of 4'-bromoacetophenone (5.00 g, 25.1 mmol) in 25 mL of ethanol was added hydroxylamine hydrochloride (2.62 g, 37.7 mmol) and pyridine (3.05 mL, 37.7 mmol). The mixture was stirred for 14 hours at 70 °C. Next, the ethanol was removed under reduced pressure to give a white slurry. The slurry was dissolved in diethyl ether (30 mL), washed with water (3 x 30 mL) and NaCl (30 mL), dried over Na_2SO_4, and concentrated to give the oxime (4.95 g, 92%) as a brown solid. The oxime was subjected to General Procedure A to give the crude nitrimine which was purified by flash column chromatography on silica gel (100% hexanes to 50:50 DCM/hexanes) to give nitrimine **2f** as a white solid (0.9307 g, 17%). R_f = 0.42 (30:70 DCM/hexanes); mp 82-84 ºC; IR (NaCl) 3064, 2840, 1553, 1401, 1325, 1294, 1004, 877, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 2.43 (s 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 132.4, 132.1, 129.4, 128.3, 16.7; HRMS (ESI): Mass calculated for $C_8H_7N_2O_2BrNa$ $[M+Na]^+$, 264.9583. Found $[M+Na]^+$, 264.9572.

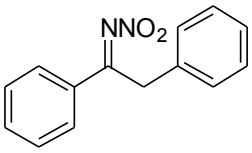
Synthesis of 2-Acetylnaphthalene Nitrimine (2e):



To a solution of 2-acetylnaphthalene (5.00 g, 29.4 mmol) in 30 mL of ethanol was added hydroxylamine hydrochloride (3.06 g, 44.1 mmol) and pyridine (3.56 mL, 44.1 mmol). The mixture was stirred for 7 hours at 60 °C. Next, the ethanol was removed under reduced pressure to give a white slurry. The slurry was dissolved in diethyl ether (30 mL), washed with water (3 x 30 mL) and NaCl (30

mL), dried over Na_2SO_4, and concentrated to give the oxime (5.34 g, 98%) as a white solid. The oxime was subjected to General Procedure A to give the crude nitrimine which was purified by flash column chromatography on silica gel (100% hexanes to 25:75 DCM/hexanes) to give nitrimine **2g** as a pale yellow solid (0.9793 g, 14%). R_f = 0.25 (25:75 DCM/hexanes); mp 89-92 ºC IR (NaCl) 3064, 2931, 1557, 1379, 1287 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 1.56 Hz, 1H), 8.00−7.89 (m, 4H), 7.65−7.56 (m, 2H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 135.6, 132.7, 130.5, 130.0, 129.3, 129.0, 128.8, 128.0, 127.3, 123.3, 16.7; HRMS (ESI): Mass calculated for $C_{12}H_{10}N_2O_2Na$ $[M+Na]^+$, 237.0628. Found $[M+Na]^+$, 237.0634.

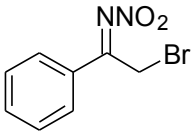
Synthesis of Deoxybenzoin Nitrimine (2f):



To a solution of hydroxylamine hydrochloride (2.65 g, 38.2 mmol) and sodium acetate trihydrate (4.34 g, 31.9 mmol) in 15 mL water was added a solution of deoxybenzoin (5.00 g, 28.4 mmol) in 15 mL of methanol. The mixture was stirred for 12 hours at 60 °C. Next, the methanol was removed under reduced pressure to give a beige slurry which was passed through a medium porosity ceramic filter, washing with water (3 x 10 mL), to give the oxime (5.38 g, 100%) as a beige powder. The oxime was subjected to General Procedure B to give the crude nitrimine which was purified by flash column chromatography on silica gel (100% hexanes to 10:90 DCM/hexanes) to give nitrimine **2h** as a white solid (0.5309 g, 23%). R_f = 0.45 (30:70 DCM/hexanes); mp 45-48 ºC; IR (NaCl) 3064, 3032, 1598, 1561, 1493, 1447, 1292, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82−7.79 (m, 2H); 7.51−7.47 (m, 1H), 7.47−7.37 (m, 2H), 7.30−7.22 (m, 5H), 4.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)

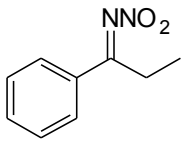
δ 170.3, 133.6, 132.9, 132.2, 129.2, 129.0, 128.8, 128.7, 127.6, 37.0; HRMS (ESI): Mass calculated for $C_{14}H_{12}N_2NaO_2$ $[M+Na]^+$, 263.0791. Found $[M+Na]^+$, 263.0795.

Synthesis of 2-Bromoacetophenone Nitrimine (2g):



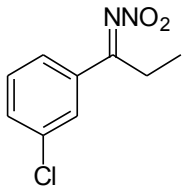
A mixture of N-bromosuccinimide (6.33 g, 33.29 mmol) and p-toluenesulfonic acid (1.18 g, 6.66 mmol) was added to acetophenone and stirred at 50 ^oC for 30 minutes. The mixture was dissolved in diethyl ether (30 mL) and washed with H_2O (3 x 30 mL), $NaHCO_3$ (30 mL), dried over Na_2SO_4, and concentrated to give the brominated ketone as a white solid (6.4077 g, 97%). To a solution of brominated ketone (3.52 g, 17.7 mmol) in ethanol (20 mL) was added hydroxylamine hydrochloride (1.84 g, 26.5 mmol) and pyridine (2.15 mL, 26.5 mmol). The reaction was stirred for 24 h at room temperature. Next, ethanol was removed under reduced pressure and the residue was dissolved in diethyl ether (30 mL), washed with H_2O (30 mL) and NaCl (30 mL), dried over Na_2SO_4, and concentrated to give the oxime as a white solid (1.30 g, 34%). The oxime was subjected to General Procedure B to give the crude nitrimine which was purified by flash column chromatography on silica gel (100% hexanes to 10:90 DCM/hexanes) to give nitrimine **2i** as a white solid (0.4006 g, 27%). R_f = 0.32 (30:70 DCM/hexanes); IR (NaCl) 3064, 3032, 1598, 1561, 1493, 1447, 1292, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97−7.94 (m, 2H), 7.63−7.59 (m, 1H), 7.51−7.47 (m, 2H), 4.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 134.4, 134.1, 129.0, 128.7, 46.1; HRMS (ESI): Mass calculated for $C_8H_7N_2O_2Br$ $[M+H]^+$, 242.9764. Found $[M+H]^+$, 242.9760.

Synthesis of Propiophenone Nitrimine (2h):



To a solution of propiophenone (4.00 g, 29.8 mmol) in 25 mL of ethanol was added hydroxylamine hydrochloride (3.11 g, 44.7 mmol) and pyridine (3.62 mL, 44.7 mmol). The mixture was stirred for 16 hours at 60 ^{o}C. Next, the ethanol was removed under reduced pressure to give a white slurry. The slurry was dissolved in diethyl ether (30 mL), washed with water (3 x 30 mL) and NaCl (30 mL), dried over Na_2SO_4, and concentrated to give the oxime (4.37 g, 98%) as a white solid. The oxime was subjected to General Procedure B to give the crude nitrimine which was purified by flash column chromatography on silica gel (100% hexanes to 25:75 DCM/hexanes) to give nitrimine **2c** as a clear, pale yellow oil (0.7125 g, 12%). R_f = 0.52 (30:70 DCM/hexanes); IR (NaCl) 3064, 2986, 2936, 1685, 1603, 1561, 1452, 1292, 1233, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.82 (m, 2H), 7.59−7.55 (m, 1H), 7.51−7.46 (m, 2H), 2.77 (q, *J* = 7.7 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 133.0, 131.8, 129.2, 128.2, 24.4, 12.9; HRMS (ESI): Mass calculated for $C_9H_{10}N_2O_2Na$ $[M+Na]^+$, 201.0634. Found $[M+Na]^+$, 201.0633.

Synthesis of 3-Chloropropiophenone Nitrimine (2i):



To a solution of 3'-chloropropiophenone (2.00 g, 11.9 mmol) in 15 mL of ethanol was added hydroxylamine hydrochloride (1.24 g, 17.8 mmol) and pyridine (1.44 mL, 17.8 mmol). The mixture was stirred for 5 hours at 50 ^{o}C. Next, the ethanol was removed under reduced pressure to give a white slurry. The slurry was dissolved in diethyl ether (30 mL), washed with water (3 x 30 mL) and NaCl (30 mL), dried over Na_2SO_4, and concentrated to give the oxime as a white solid. The oxime was subjected to General Procedure A to give the crude nitrimine which was

purified by flash column chromatography on silica gel (30:70 DCM/hexanes) to give nitrimine **2b** as a clear, colorless oil (0.3328 g, 13%). R_f = 0.52 (30:70 DCM/hexanes); IR (NaCl) 3073, 2986, 2940, 2877, 1602, 1561, 1465, 1415, 1292, 1233, 886, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (t, *J* = 1.8 Hz, 1 H), 7.71 (qd, *J* = 1.0 Hz, 7.9 Hz, 1 H), 7.55 (qd, *J* = 1.0 Hz, 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 2.75 (q, *J* = 7.7 Hz, 2H), 1.27 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 135.5, 133.7, 133.0, 130.5, 128.3, 126.4, 24.5, 12.8; HRMS (ESI): Mass calculated for $C_9H_9N_2O_2ClNa$ $[M+Na]^+$, 235.0245. Found $[M+Na]^+$, 235.0248.

Procedure for the Preparation of Coupled Alkene Products (3a-3m):

General Procedure A: Cross-coupling of nitrimines and indoles with Schreiner's urea in toluene

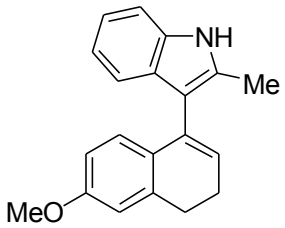
To a 4 ml, glass, oven-dried, screw-capped vial fitted with a Teflon-septum cap and stir bar was added acetophenone nitrimine **2d** (0.0400 g, 0.244 mmol), Schreiner's urea (0.0236 g, 0.0487 mmol), and 4 Å molecular sieves in that order. The vial was evacuated and filled with N_2 three times and then *N*-methylindole (121.6 μL, 0.975 mmol), toluene (0.50 mL) and pyridine (39.4 μL, 0.487 mmol) were added. The mixture was heated at 50 ^oC for 48 h. The reaction was immediately purified by flash column chromatography (100% hexanes to 5:95 diethyl ether/hexanes) on silica gel to give the coupled product.

General Procedure B: Cross-coupling of nitrimines and indoles

To a 4 ml, glass, oven-dried, screw-capped vial fitted with a Teflon-septum cap and stir bar was added acetophenone nitrimine **2d** (0.0400 g, 0.244 mmol), 2-methylindole (0.128 g, 0.975 mmol), and 4 Å molecular sieves in that order. The vial was evacuated and filled with N_2 three times and then pyridine (39.4 μL, 0.487 mmol) was added in one

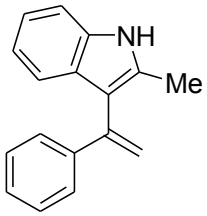
portion. The mixture was heated at 50 °C for 24 h. The reaction was immediately purified by flash column chromatography (100% hexanes to 15:85 diethyl ether/hexanes) on silica gel to give the coupled product.

Synthesis of 3-(6-methoxy-3,4-dihydronaphthalen-1-yl)-2-methyl-1*H*-indole (2a):



6-Methoxy-1-tetralone nitrimine (0.0400 g, 0.136 mmol), 2-methylindole (0.0715 g, 0.545 mmol), 1,1,1,3,3,3-hexafluoroisopropanol (286.9 µL, 2.73 mmol), and pyridine (22.0 µL, 0.273 mmol) were subjected to General Procedure A for 24 h. The reaction mixture was immediately purified by flash column chromatography on silica gel (100% hexanes to 20:80 DCM/hexanes) to give the coupled product as a yellow solid (0.0425 g, 81%). R_f = 0.25 (20:80 diethyl ether/hexanes); IR (NaCl) 3397, 3051, 2933, 2828, 2161, 1704, 1605, 1488, 1455, 1429, 1246, 1154, 1108, 1030, 827, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.32−7.28 (m, 2H), 7.11−7.09 (m, 1H), 7.01−6.99 (m, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 2.7 Hz, 1H), 6.55 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.97 (t, *J* = 4.6 Hz, 1H), 3.79 (s, 3H), 2.94−2.86 (m, 2H), 2.50−2.44 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 138.2, 135.4, 132.4, 131.5, 129.0, 128.7, 126.9, 126.7. 121.2, 119.7, 119.5, 113.8, 113.1, 110.8, 110.2, 55.4, 29.0, 23.7, 12.7; HRMS (ESI): Mass calculated for $C_{20}H_{20}NO$ $[M+H]^+$, 290.1539. Found $[M+H]^+$, 290.1525.

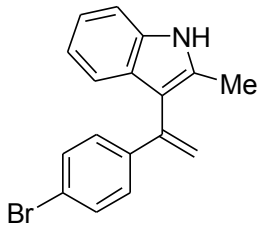
Synthesis of 2-methyl-3-(1-phenylvinyl)-1*H*-indole (2c):



Acetophenone nitrimine (0.0400 g, 0.244 mmol), 2-methylindole (0.128 g, 0.975 mmol), and pyridine (39.4 µL, 0.487 mmol) were subjected to General Procedure B for 24 h. The reaction was

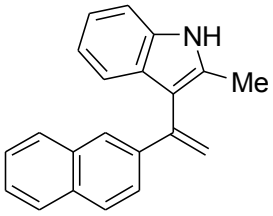
immediately purified by flash column chromatography on silica gel (100% hexanes to 15:85 diethyl ether/hexanes) to give the coupled product as a white solid (0.0392 g, 69%). R_f = 0.27 (20:80 diethyl ether/hexanes); IR (NaCl) 3398, 3051, 2922, 2854, 1654, 1611, 1561, 1456, 1264, 1215, 1073, 1023, 893, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 1H), 7.42−7.38 (m, 2H), 7.32−7.27 (m, 4H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.13−7.09 (m, 1H), 7.01−6.97 (m, 1H), 5.74 (d, *J* = 1.6 Hz, 1H), 5.33 (d, *J* = 1.6 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 142.0, 135.3, 133.2, 128.6, 128.3, 127.6, 127.4, 121.4, 119.8, 119.8, 115.0, 114.2, 110.2, 12.9; HRMS (ESI): Mass calculated for $C_{17}H_{15}NNa$ $[M+Na]^+$, 256.1097. Found $[M+Na]^+$, 256.1093.

Synthesis of 3-(1-(4-bromophenyl)vinyl)-2-methyl-1*H*-indole (2d):



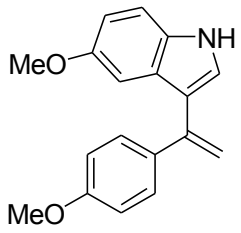
4'-Bromoacetophenone nitrimine (0.0400 g, 0.165 mmol), 2-methylindole (0.0863 g, 0.658 mmol), and pyridine (26.6 μL, 0.329 mmol) were subjected to General Procedure B at 50 °C for 24 h. The crude product was purified by flash column chromatography on silica gel (100% hexanes to 15:85 diethyl ether/hexanes) to give the coupled product as a white solid (0.0396 g, 77%). R_f = 0.25 (20:80 diethyl ether/hexanes); IR (NaCl) 3690, 3452, 3055, 2986, 1424, 1265, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.42−7.41 (m, 2H), 7.30−7.26 (m, 3H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.13−7.09 (m, 1H), 7.01−6.97 (m, 1H), 5.71 (d, *J* = 1.6 Hz, 1H), 5.33 (d, *J* = 1.6 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 140.9, 135.3, 133.3, 131.4, 129.1, 128.3, 121.6, 121.5, 119.9, 119.7, 115.5, 113.7, 110.3, 13.0; HRMS (ESI): Mass calculated for $C_{17}H_{15}NBr$ $[M+H]^+$, 312.0382. Found $[M+H]^+$, 312.0373.

Synthesis of 2-methyl-3-(1-(naphthalen-2-yl)vinyl)-1H-indole (2e):



2-Acetylnaphthalene nitrimine (0.0400 g, 0.187 mmol), 5-methoxyindole (0. 0980 g, 0.747 mmol), and pyridine (30.2 μL, 0.374 mmol) were subjected to General Procedure B at 50 °C for 24 h. The reaction mixture was purified by flash column chromatography on silica gel (100% hexanes to 40:60 diethyl ether/hexanes) to give the coupled product as a yellow oil (0.0466 g, 88%). R_f = 0.25 (20:80 diethyl ether/hexanes); mp 133-134 ºC; IR (NaCl) 3456, 3052, 2982, 1603, 1565, 1424, 1264, 892, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.83−7.74 (m, 4H), 7.58 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.45−7.43 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.14−7.10 (m, 1H), 7.00−6.96 (m, 1H), 5.87 (d, *J* = 2.0 Hz, 1H), 5.44 (d, *J* = 1.6 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 139.5, 135.3, 133.6, 133.3, 133.1, 128.7, 128.4, 127.8, 127.7, 126.3, 126.1, 125.9, 125.8, 121.4, 119.9, 119.8, 115.7, 114.2, 110.3, 13.0; HRMS (ESI): Mass calculated for $C_{21}H_{18}N$ $[M+H]^+$, 284.1434. Found $[M+H]^+$, 284.1435.

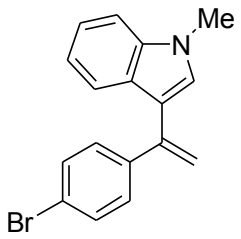
Synthesis of 5-methoxy-3-(1-(4-methoxyphenyl)vinyl)-1*H*-indole (2f):



4'-Methoxyacetophenone nitrimine (0.0400 g, 0.206 mmol), 5-methoxyindole (0.108 g, 0.824 mmol), and pyridine (33.3 μL, 0.412 mmol) were subjected to General Procedure B at 50 °C for 24 h. The reaction mixture was purified by flash column chromatography on silica gel (100% Hexanes to 40:60 diethyl ether/hexanes) to give the coupled product as a yellow oil (0.0466 g, 81%). R_f = 0.33 (30:70 ethyl acetate/hexanes); IR (NaCl) 3425, 2954, 2918, 2854, 1683, 1612, 1565, 1453, 1406, 1312, 1259, 1183, 1095, 1053, 877, 794

cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.43−7.39 (m, 2H), 7.28 (dd, *J* = 8.8, 0.4 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.88−6.86 (m, 3H), 5.45 (d, *J* = 1.6 Hz, 1H), 5.37 (d, *J* = 1.6 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 154.5, 142.8, 134.9, 131.8, 129.3, 127.0, 125.0, 118.3, 113.6, 112.6, 112.0, 110.7, 102.9, 56.0, 55.5; HRMS (ESI): Mass calculated for $C_{18}H_{17}NO_2Na$ $[M+Na]^+$, 302.1151. Found $[M+Na]^+$, 302.1154.

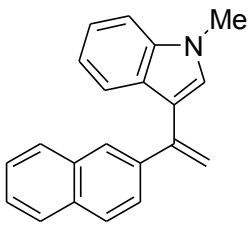
Synthesis of 3-(1-(4-bromophenyl)vinyl)-1-methyl-1H-indole (2g):



4'-Bromoacetophenone nitrimine (0.0400 g, 0.165 mmol), *N*-methylindole (82.2 μL, 0.658 mmol), and pyridine (26.6 μL, 0.329 mmol) were subjected to General Procedure A at 50 ^{o}C for 48 h. The reaction mixture was purified by flash column chromatography on silica gel (100% hexanes to 5:95 diethyl ether/hexanes) to give the coupled product as a white solid (0.0360 g, 70%).

R_f = 0.40 (5:95 diethyl ether/hexanes); IR (NaCl) 3051, 2933, 1605, 1533, 1475, 1383, 1233, 1082, 1004, 906, 827, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.47−7.44 (m, 2H), 7.36−7.33 (m, 3H), 7.27−7.23 (m, 1H), 7.12−7.08 (m, 1H), 6.96 (s, 1H), 5.56 (d, *J* = 1.2 Hz, 1H), 5.36 (d, *J* = 1.6, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 141.7, 137.6, 131.3, 130.0, 129.2, 126.7, 122.1, 121.7, 120.9, 120.0, 116.1, 112.1, 109.6, 33.0; HRMS (ESI): Mass calculated for $C_{17}H_{15}NBr$ $[M+H]^+$, 312.0382. Found $[M+H]^+$, 312.0375.

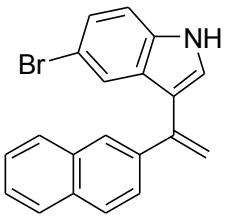
Synthesis of 2-methyl-3-(1-(naphthalen-2-yl)vinyl)-1*H*-indole (2h):



2-Acetylnaphthalene (0.0400 g, 0.187 mmol), 2-methylindole (0.0980 g, 0.747 mmol), and pyridine (30.2 μL, 0.373 mmol) were

subjected to General Procedure A at 50 °C for 48 h. The crude product was purified by flash column chromatography on silica gel (100% hexanes to 5:95 diethyl ether/hexanes) to give the coupled product as a white solid (0.0408 g, 77%). R_f = 0.33 (5:95 diethyl ether/hexanes); IR (NaCl) 3054, 2986, 1423, 1265, 896, 740, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.0 Hz, 1H), 7.86−7.79 (m, 3H), 7.62 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.57 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.49−7.45 (m, 2H), 7.37−7.34 (m, 1H), 7.27−7.23 (m, 1H), 7.11−7.07 (m, 1H), 7.00 (s, 1H), 5.65 (d, *J* = 1.6 Hz, 1H), 5.50 (d, *J* = 1.6 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 140.3, 137.6, 133.5, 133.2, 129.3, 128.3, 127.7, 127.6, 127.0, 127.0, 126.8, 126.1, 125.9, 122.0, 121.0, 119.9, 116.6, 112.3, 109.5, 33.0; HRMS (ESI): Mass calculated for $C_{21}H_{18}N$ $[M+H]^+$, 284.1434. Found $[M+H]^+$, 284.1444.

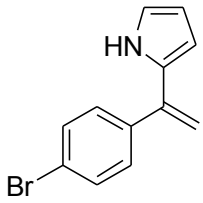
Synthesis of 5-bromo-3-(1-(naphthalen-2-yl)vinyl)-1*H*-indole (2i):



2-Acetylnaphthalene nitrimine (0.0400 g, 0.187 mmol), 5-bromoindole (0.1464 g, 0.747 mmol), and pyridine (30.2 μL, 0.373 mmol) were subjected to General Procedure A at 50 °C for 48 h. The reaction mixture was purified by flash column chromatography on silica gel (100% hexanes to 20:80 diethyl ether/hexanes) to give the coupled product as a white solid (0.0260 g, 40%). R_f = 0.21 (20:80 diethyl ether/hexanes); mp 193-195 ºC; IR (NaCl) 3426, 3152, 3058, 2986, 1797, 1653, 1604, 1559, 1456, 1438, 1379, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.90−7.75 (m, 5H), 7.57 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.49−7.46 (m, 2H), 7.33−7.28 (m, 2H), 7.14 (d, *J* = 2.6 Hz, 1H), 5.64 (d, *J* = 1.3 Hz, 1H), 5.60 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 139.6, 135.3, 133.5, 133.2, 128.4, 128.3, 127.8, 127.7, 126.9, 126.4, 126.3, 126.1, 125.6, 125.5, 123.3, 118.0,

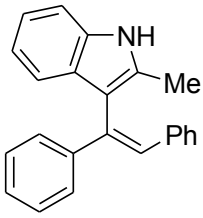
113.8, 113.6, 112.8; HRMS (ESI): Mass calculated for $C_{20}H_{15}NBr$ $[M+H]^+$, 348.0382. Found $[M+H]^+$, 348.0373.

Synthesis of 2-(1-(4-bromophenyl)vinyl)-1*H*-pyrrole (2j):



4'-Bromoacetophenone nitrimine (0.0400 g, 0.165 mmol), pyrrole (45.7 μL, 0.658 mmol), and pyridine (26.6 μL, 0.329 mmol) were subjected to General Procedure B at 50 °C for 48 h. The reaction mixture was purified by flash column chromatography on silica gel (100% hexanes to 30:70 DCM/hexanes) to give the coupled product as a pale yellow oil (0.0212 g, 52%). R_f = 0.30 (30:70 DCM/hexanes); IR (NaCl) 3534, 3163, 3001, 2942, 1438, 1373, 1039, 915, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.50−7.48 (m, 2H), 7.33−7.31 (m, 2H), 6.82−6.80 (m, 1H), 6.24−6.18 (m, 2H), 5.34 (s, 1H), 5.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 139.7, 131.6, 130.2, 122.2, 119.0, 109.8, 109.3, 109.3; HRMS (ESI): Mass calculated for $C_{12}H_{11}NBr$ $[M+H]^+$, 248.0069. Found $[M+H]^+$, 248.0063.

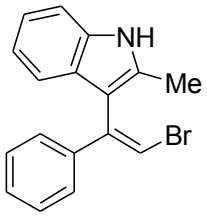
Synthesis of 3-(1,2-diphenylvinyl)-2-methyl-1*H*-indole (3j):



Deoxybenzoin nitrimine (0.0400 g, 0.167 mmol), 2-methylindole (0.0874 g, 0.666 mmol), and pyridine (26.3 μL, 0.333 mmol) were subjected to General Procedure B at 50 °C for 24 h. The crude product was purified by flash column chromatography on silica gel (100% hexanes to 10:90 diethyl ether/hexanes) to give the coupled product as a 5:1 mixture of E/Z isomers (0.0325 g, 63%). R_f = 0.15 (10:90 diethyl ether/hexanes); IR (NaCl) 3401, 3055, 2987, 1423, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (br s, 1H), 7.44−7.42 (m, 1H), 7.33−7.24 (m, 4H), 7.13−7.03 (m, 9H), 6.98−6.92 (m, 1H), 1.96 (s,

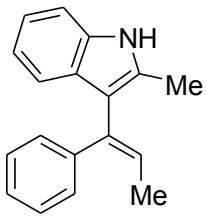
3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 138.7, 135.8, 135.2, 133.1, 129.6, 128.8, 128.6, 128.3, 128.2, 127.5, 127.3, 126.5, 121.3, 120.1, 119.7, 112.0, 110.2, 12.6; HRMS (ESI): Mass calculated for $C_{23}H_{19}NNa$ $[M+Na]^+$, 332.1410. Found $[M+Na]^+$, 332.1403.

Synthesis of (Z)-3-(2-bromo-1-phenylvinyl)-2-methyl-1*H*-indole (3k):



2-Bromoacetophenone nitrimine (0.0300 g, 0.1234 mmol), 2-methylindole (0.0648 g, 0.494 mmol), and pyridine (20.0 μL, 0.247 mmol) were subjected to General Procedure A at 50 °C for 24 h. The reaction mixture was purified by flash column chromatography on silica gel (100% hexanes to 5:95 diethyl ether/hexanes) to give the coupled product. R_f = 0.25 (20:80 diethyl ether/hexanes); IR (NaCl) 3419, 3150, 1635, 1465, 1380, 1097, 906, 729, 651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): the compound exists as a mixture of E/Z isomers. Signals corresponding to both isomers δ 8.03, (br s, 1H), 7.93 (br s, 1H), 7.47−7.45 (m, 2H), 7.36−7.27 (m, 10 H), 7.18 (d, *J* = 8 Hz, 1H), 7.13−7.07 (m, 3H), 7.00−6.96 (m, 2H), 6.70 (s, 1H), 6.41 (s, 1H), 2.30 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 138.2, 136.7, 135.1, 133.5, 129.8, 128.6, 128.2, 128.1, 128.1, 127.9, 127.3, 121.7, 121.5, 120.2, 119.9, 119.3, 116.9, 115.3, 113.3, 110.4, 110.4, 110.0, 13.1, 12.8; HRMS (ESI): Mass calculated for $C_{17}H_{15}NBr$ $[M+H]^+$, 312.0382. Found $[M+H]^+$, 312.0380.

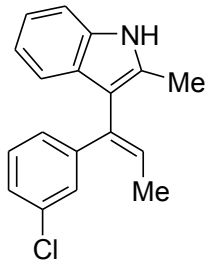
Synthesis of 2-methyl-3-(1-phenylprop-1-en-1-yl)-1*H*-indole (3l):



Propiophenone nitrimine (0.0400 g, 0.225 mmol), 2-methylindole (0.118 g, 0.898 mmol), and pyridine (36.3 μL, 0.449 mmol) were subjected to General Procedure B at 50 °C for 24 h. The reaction mixture was purified by flash column chromatography on silica gel

(100% hexanes to 20:80 diethyl ether/hexanes) to give the coupled product as a clear oil (0.0315 g, 57%). R_f = 0.33 (20:80 diethyl ether/hexanes); IR (NaCl) 3467, 3054, 2986, 1655, 1459, 1265, 909, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): the compound exists as a 6:1 mixture of E/Z isomers. Signals corresponding to the major isomer δ 7.79 (br s, 1H), 7.34−7.20 (m, 7H), 7.10−7.06 (m, 1H), 6.99−6.95 (m, 1H), 5.96 (q, *J* = 7.1 Hz, 1H), 2.20 (s, 3H), 1.96 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 135.3, 135.1, 132.3, 129.8, 128.7, 128.2, 128.0, 126.8, 126.6, 125.3, 121.2, 119.6, 119.5, 116.7, 110.1, 15.5, 12.9; HRMS (ESI): Mass calculated for $C_{18}H_{18}N$ $[M+H]^+$, 248.1434. Found $[M+H]^+$, 248.1432.

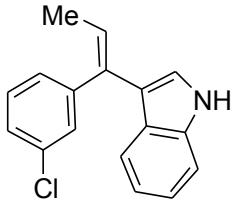
Synthesis of 3-(1-(3-chlorophenyl)vinyl)-2-methyl-1*H*-indole (3m):



3'-Chloropropiophenone nitrimine (0.0400 g, 0.188 mmol), 2-methylindole (0.0987 g, 0.7525 mmol), and pyridine (30.4 μL, 0.376 mmol) were subjected to General Procedure A at 50 °C for 24 h. The reaction mixture was purified by flash column chromatography on silica gel (100% hexanes to 20:80 diethyl ether/hexanes) to give the coupled product as an orange oil (0.0435g, 82%). R_f = 0.27 (20:80 diethyl ether/hexanes); IR (NaCl) 3355.0, 3054, 2987, 1655, 1459, 1265, 909, 735, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): the compound exists as a 20:1 mixture of E/Z isomers. Signals corresponding to the major isomer δ 7.83 (br s, 1H), 7.27−7.20 (m, 5H), 7.17−7.14 (m, 1H), 7.11−7.07 (m, 1H), 7.00−6.96 (m, 1H), 5.97 (q, *J* = 7.1 Hz, 1H), 2.21 (s, 3H), 1.94 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 135.1, 134.2, 133.9, 132.4, 129.7, 129.3, 128.5, 128.0, 126.8, 126.5, 121.3, 119.8, 119.4, 116.1, 110.2, 15.5, 12.9; HRMS (ESI): Mass calculated for $C_{18}H_{16}NClNa$ $[M+Na]^+$, 304.0863. Found $[M+Na]^+$, 304.0855.

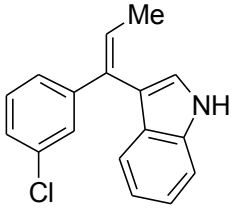
Conditions for controlling *E/Z* selectivity:

Synthesis of (*E*)-3-(1-(3-chlorophenyl)prop-1-en-1-yl)-1*H*-indole *E*-(3n):



3'-Chloropropiophenone nitrimine (0.0400 g, 0.188 mmol), indole (0.0882 g, 0.7525 mmol), and pyridine (30.4 μL, 0.376 mmol) were subjected to General Procedure A at 50 ^{o}C for 24 h. The reaction mixture was purified by purified by flash column chromatography on silica gel (100% hexanes to 20:80 diethyl ether/hexanes) to give the coupled product as a pale yellow oil (62%). R_f = 0.27 (20:80 diethyl ether/hexanes); IR (NaCl) 3355.0, 3054, 2987, 1655, 1459, 1265, 909, 735, 650 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): the compound exists as a mixture of E/Z isomers. Signals corresponding to the major isomer δ 7.96 (br s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.29 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.25−7.21 (m, 2H), 7.14−7.07 (m, 3H), 7.04−7.00 (m, 1H), 6.76 (d, *J* = 2.5 Hz, 1H), 6.22 (q, *J* = 7.1 Hz, 1H), 1.73 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 136.8, 135.3, 134.0, 129.9, 129.5, 128.2, 127.0, 126.8, 123.7, 122.4, 122.3, 120.7, 120.2, 119.9, 111.4, 15.4; HRMS (ESI): Mass calculated for $C_{17}H_{14}NClNa$ $[M+Na]^+$, 290.0707. Found $[M+Na]^+$, 290.0698.

Synthesis of (*Z*)-3-(1-(3-chlorophenyl)prop-1-en-1-yl)-1*H*-indole *Z*-(3n):

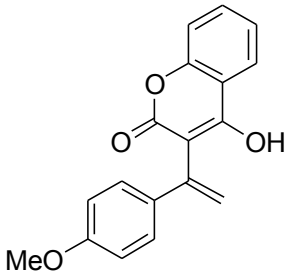


3'-Chloropropiophenone nitrimine (0.0400 g, 0.188 mmol), indole (0.0264 g, 0.226 mmol), and pyridine (30.4 μL, 0.376 mmol) were stirred in toluene (0.07 mL) at room temperature for 48 h to yield 59% of the *Z* isomer . Yield was determined by ^{1}H NMR using ferrocene as an internal standard.

General Procedure for cross-coupling of nitrimines and 4-hydroxycoumarin:

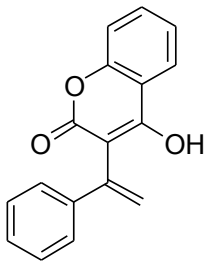
To a 4 ml, glass, oven-dried, screw-capped vial fitted with a Teflon-septum cap and stir bar was added acetophenone nitrimine (**2c**) (0.0300 g, 0.183 mmol), 4-hydroxycoumarin (0.0593 g, 0.365 mmol), and 4 Å molecular sieves in that order. The vial was evacuated and filled with N_2 three times and then DMSO (0.18 mL) and pyridine (14.8 µl, 0.183 mmol) was added in one portion. The mixture was stirred at room temperature for 24 h. The reaction was immediately purified by flash column chromatography on silica gel.

Synthesis of 4-hydroxy-3-(1-(4-methoxyphenyl)vinyl)-2*H*-chromen-2-one (6a):



The compound was isolated by flash column chromatography on silica gel (100% hexanes to 30:70 ethyl acetate/hexanes) to give a white solid (0.0381 g, 60%). R_f = 0.40 (40:60 ethyl acetate/hexanes); mp 100-103 ºC; IR (NaCl) 3055, 2987, 1709, 1626, 1514, 1424, 1264, 896, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, J = 7.9, 1.4 Hz, 1H), 7.62−7.58 (m, 1H), 7.41−7.32 (m, 4H), 6.89−6.86 (m, 2H), 6.72 (br s, 1H), 6.04 (d, J = 0.8 Hz, 1H), 5.47 (d, J = 0.8 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 160.5, 160.2, 153.3, 138.5, 132.8, 130.0, 127.7, 124.2, 124.0, 118.0, 116.9, 114.8, 114.4, 106.3, 55.5; HRMS (ESI): Mass calculated for $C_{18}H_{15}O_4$ $[M+H]^+$, 295.0965. Found $[M+H]^+$, 295.0963.

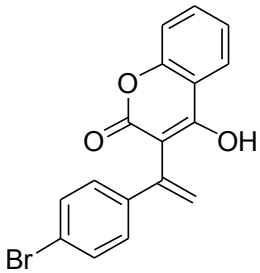
Synthesis of 4-hydroxy-3-(1-phenylvinyl)-2*H*-chromen-2-one (6d):



The compound was isolated by flash column chromatography on silica gel (100% hexanes to 30:70 ethyl acetate/hexanes) to give a cloudy liquid (0.0184 g, 57%). R_f = 0.33 (40:60 ethyl acetate/hexanes); IR (NaCl) 3687, 3054, 2988, 1706, 1652, 1571, 1424, 1265, 898, 739 cm^-

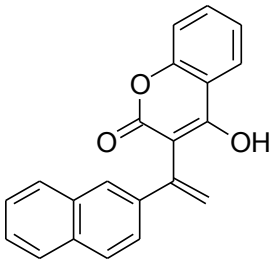
[1]; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.91 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.63−7.58 (m, 1H), 7.47−7.45 (m, 2H), 7.39-7.32 (m, 5H), 6.69 (br s, 1H), 6.14 (d, *J* = 1.2 Hz, 1H), 5.58 (d, *J* = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 160.2, 153.3, 139.3, 137.6, 132.8, 129.2, 129.0, 126.3, 124.3, 124.0, 120.0, 116.9, 114.7, 106.2; HRMS (ESI): Mass calculated for $C_{17}H_{13}O_3$ $[M+H]^+$, 265.0859. Found $[M+H]^+$, 265.0847.

Synthesis of 3-(1-(4-bromophenyl)vinyl)-4-hydroxy-2*H*-chromen-2-one (6b):



The compound was isolated by flash column chromatography on silica gel (100% hexanes to 40:60 ethyl acetate/hexanes) to give a white solid (0.0534 g, 94%). R_f = 0.33 (40:60 ethyl acetate/hexanes); mp 164-165 ºC; IR (NaCl) 3474, 3052, 2983, 1704, 1618, 1566, 1492, 1418, 1264, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 1.4 Hz, 1H), 7.61 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.38−7.30 (m, 4H), 6.78 (br s, 1H), 6.12 (s, 1H), 5.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 160.5, 153.3, 138.6, 136.7, 133.0, 132.1, 127.9, 124.3, 124.1, 123.3, 120.3, 116.9, 114.6, 105.6; HRMS (ESI): Mass calculated for $C_{17}H_{12}BrO_3$ $[M+H]^+$, 342.9964. Found $[M+H]^+$, 342.9957.

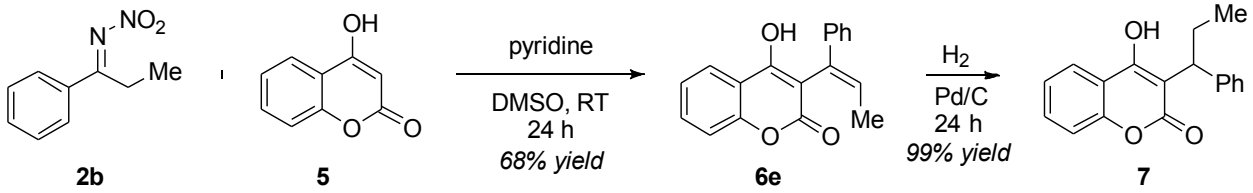
Synthesis of 4-hydroxy-3-(1-(naphthalen-2-yl)vinyl)-2*H*-chromen-2-one (6c):



The compound was isolated by flash column chromatography on silica gel (100% hexanes to 30:70 ethyl acetate/hexanes) to give a white solid (0.0420 g, 72%). R_f = 0.50 (30:70 ethyl acetate/hexanes); mp 181-183 ºC; IR (NaCl) 3293, 3057, 2933, 2861, 1677, 1605, 1560, 1494, 1272, 1207, 1030, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.85−7.78 (m, 4H), 7.66−7.61 (m, 2H), 7.48−7.45 (m, 2H), 7.41−7.35 (m, 2H), 6.89 (br s, 1H), 6.27 (d, *J* = 0.5 Hz, 1H), 5.67 (d, *J* = 0.5 Hz,

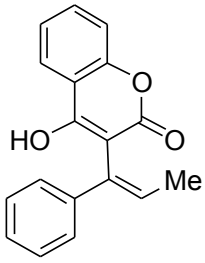
1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 160.4, 153.4, 139.1, 134.9, 133.7, 133.5, 132.9, 128.9, 128.6, 127.8, 126.7, 126.6, 125.7, 124.3, 124.0, 123.8, 120.5, 116.9, 114.8, 106.2; HRMS (ESI): Mass calculated for $C_{21}H_{14}O_3Na$ $[M+Na]^+$, 337.0835. Found $[M+Na]^+$, 337.0822.

Procedure for the Preparation of Phenprocoumon 7:



2b **5** **6e** **7**

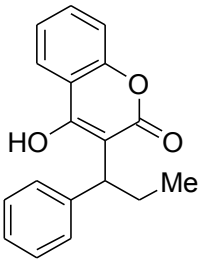
Synthesis of (Z)-4-hydroxy-3-(1-phenylprop-1-en-1-yl)-2*H*-chromen-2-one (6e):



To a 4 ml, glass, oven-dried, screw-capped vial fitted with a Teflon-septum cap and stir bar was added propiophenone nitrimine (**2b**) (0.0300 g, 0.183 mmol), 4-hydroxycoumarin **5** (0.0959 g, 0.731 mmol), and 4 Å molecular sieves in that order. The vial was evacuated and filled with N_2 three times and then DMSO (0.18 mL) and pyridine (29.6 µl, 0.365 mmol) was added in one portion. The mixture was stirred at room temperature for 24 h. The reaction was immediately purified by flash column chromatography on silica gel (100% hexanes to 20:80 ethyl acetate/hexanes) to give a clear liquid (0.0319 g, 68%). R_f = 0.25 (20:80 ethyl acetate/hexanes); IR (NaCl) 3051, 2983, 1709, 1623, 1418, 1263, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (ddd, *J* = 0.4, 2.0, 8.0 Hz, 1H), 7.63−7.59 (m, 1H), 7.41−7.30 (m, 8H), 6.62 (q, *J* = 6.8 Hz, 1H), 1.84 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 153.6, 138.7, 132.7, 131.5, 130.8, 129.5, 128.9, 128.2, 126.0,

124.2, 123.8, 116.9, 114.7, 103.7, 15.9; HRMS (ESI): Mass calculated for $C_{18}H_{14}O_3Na$ $[M+Na]^+$, 301.0835. Found $[M+Na]^+$, 301.0839.

Synthesis of 4-hydroxy-3-(1-phenylpropyl)-2*H*-chromen-2-one (7):



A mixture of **6e** (0.0400 g, 0.144 mmol) and 10% Pd/C (0.0040 g, 0.0374 mmol) in ethyl acetate (0.70 mL) was stirred under 1 atm of H_2 for 24 h, then filtered through Celite. The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (100% hexanes to 30:70 ethyl acetate/hexanes) to give a white solid (0.0399 g, 99%). R_f = 0.48 (30:70 ethyl acetate/hexanes); mp 174-176 ºC; IR (NaCl) 3051, 2983, 1709, 1623, 1418, 1263, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.53-7.47 (m, 3H), 7.44-7.40 (m, 2H), 7.34-7.30 (m, 2H), 7.24-7.20 (m, 1H), 6.09 (br s, 1H), 4.54 (t, *J* = 7.6 Hz, 1H), 2.27-2.24 (m, 1H) 2.22-2.09 (m, 1H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 159.9, 152.8, 141.2, 132.0, 129.9, 127.9, 127.8, 124.0, 122.9, 116.6, 116.1, 109.1, 41.8, 24.1, 12.4; HRMS (ESI): Mass calculated for $C_{18}H_{16}O_3Na$ $[M+Na]^+$, 303.0992. Found $[M+Na]^+$, 303.0991.

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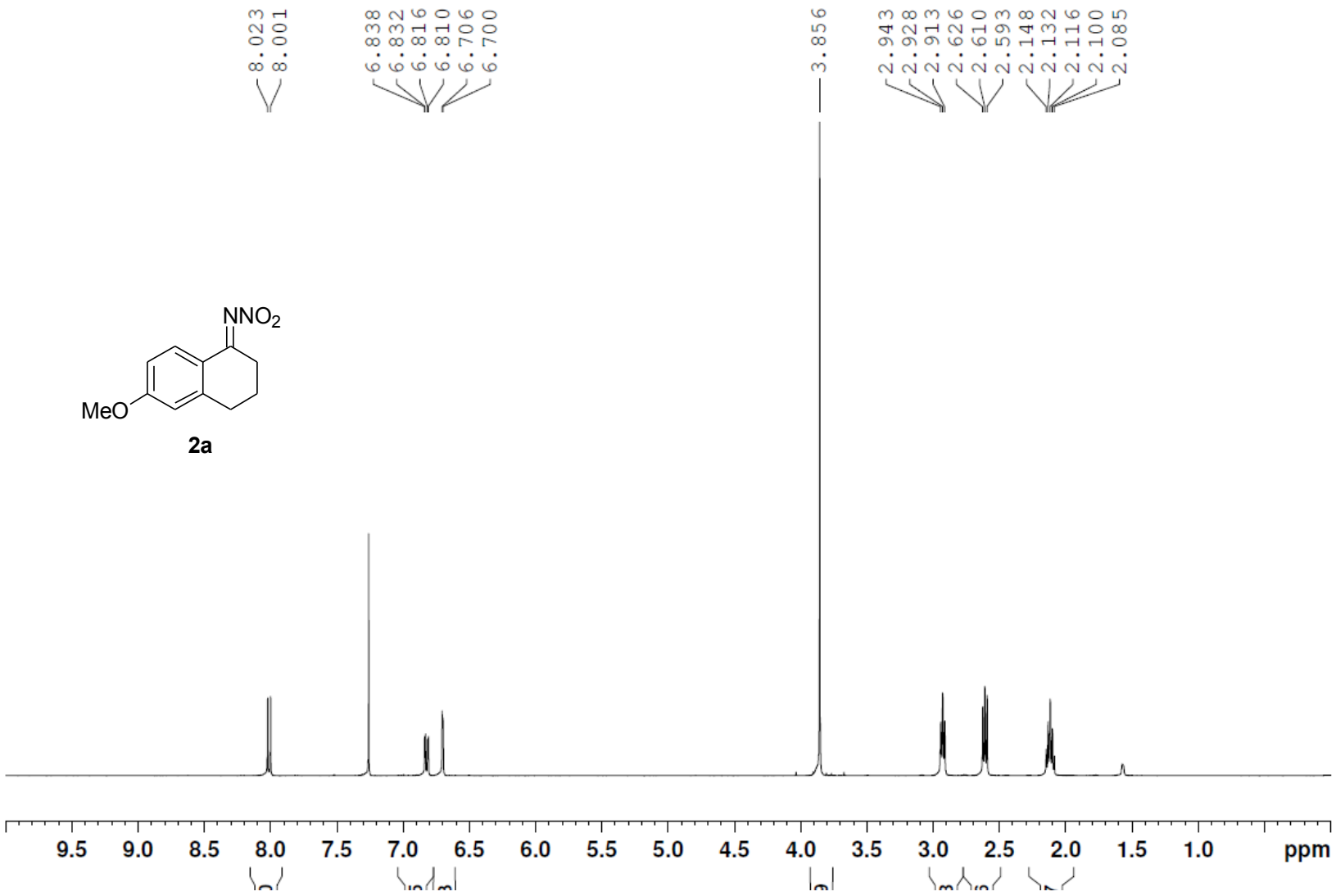
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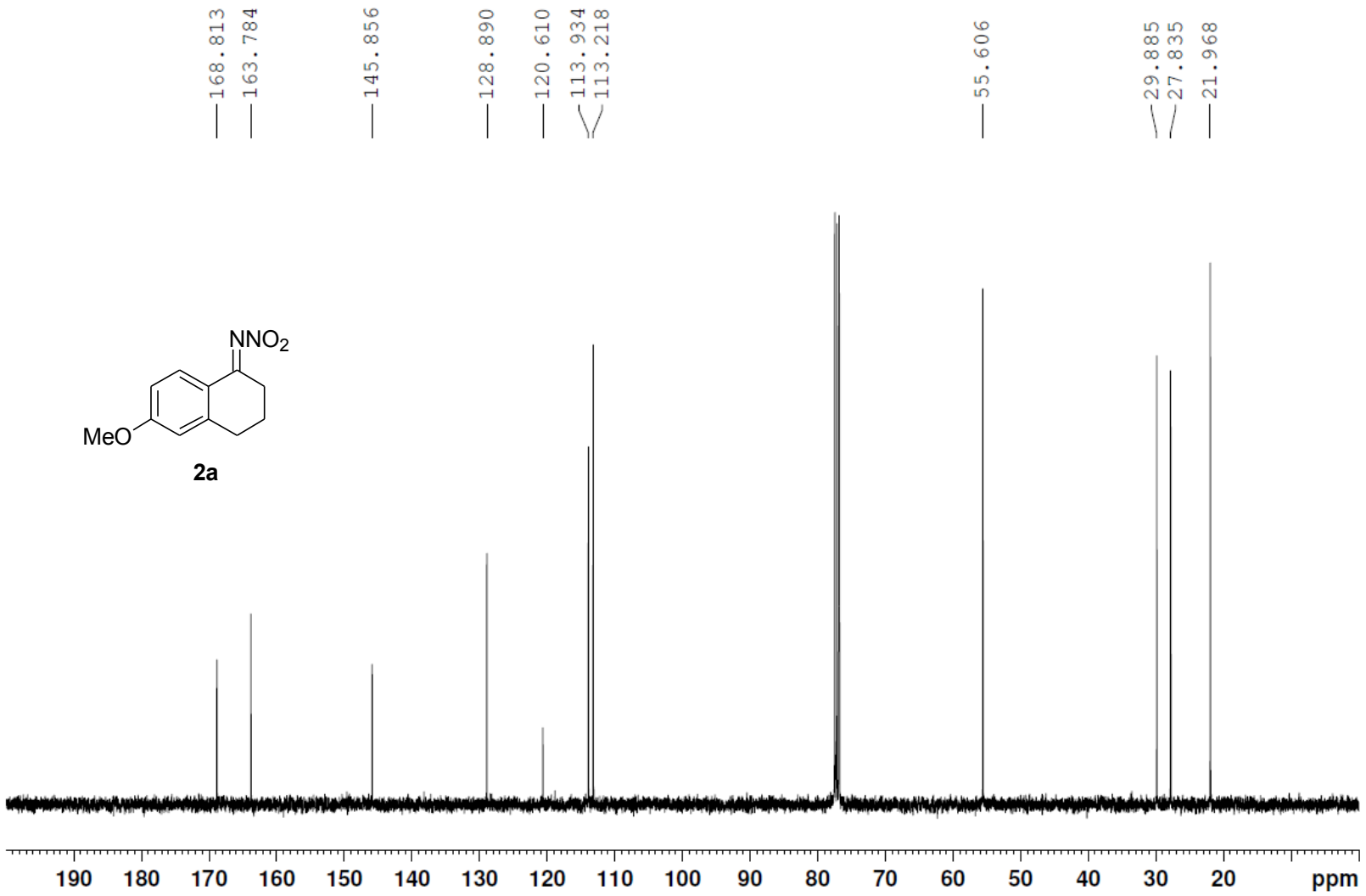
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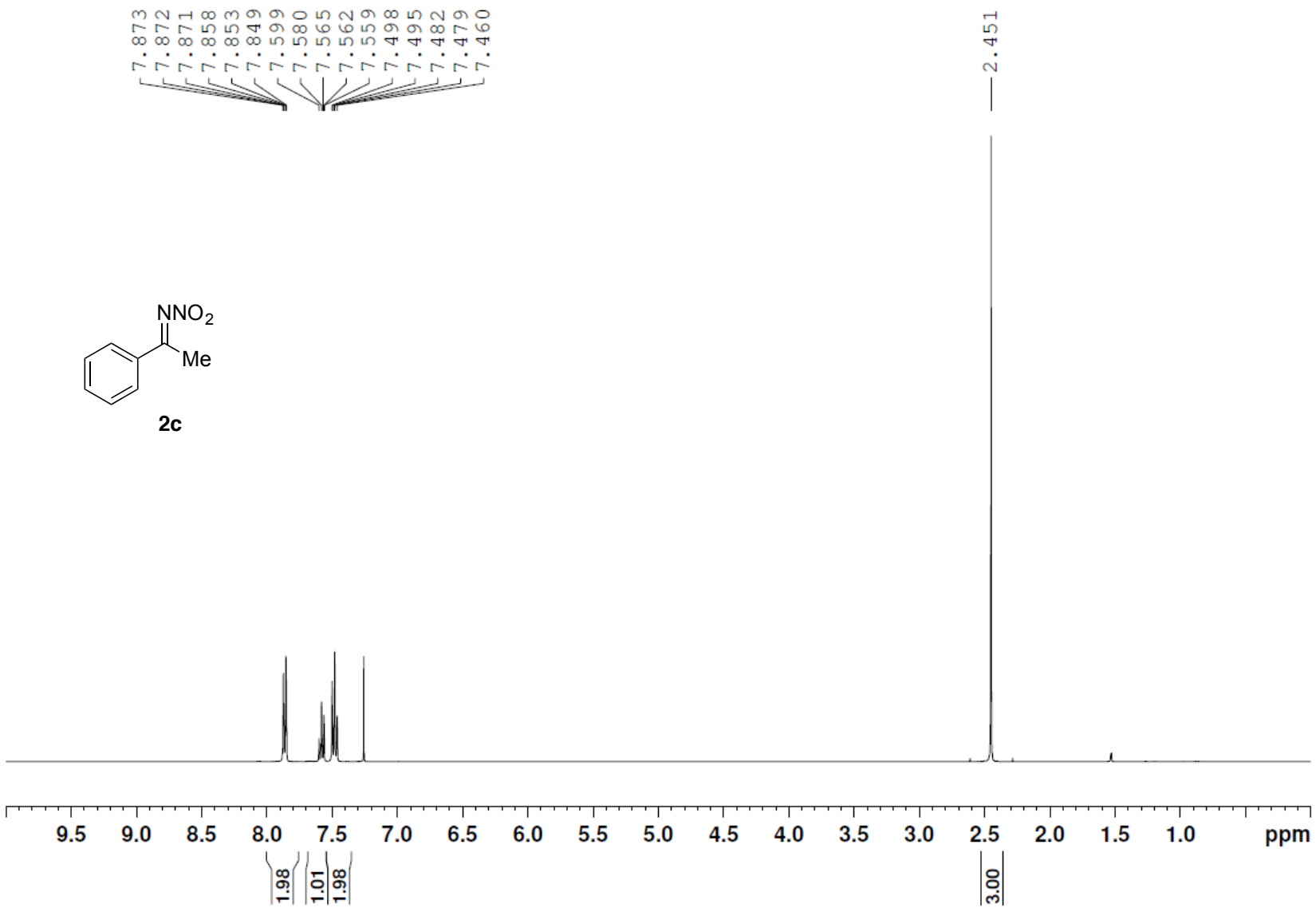
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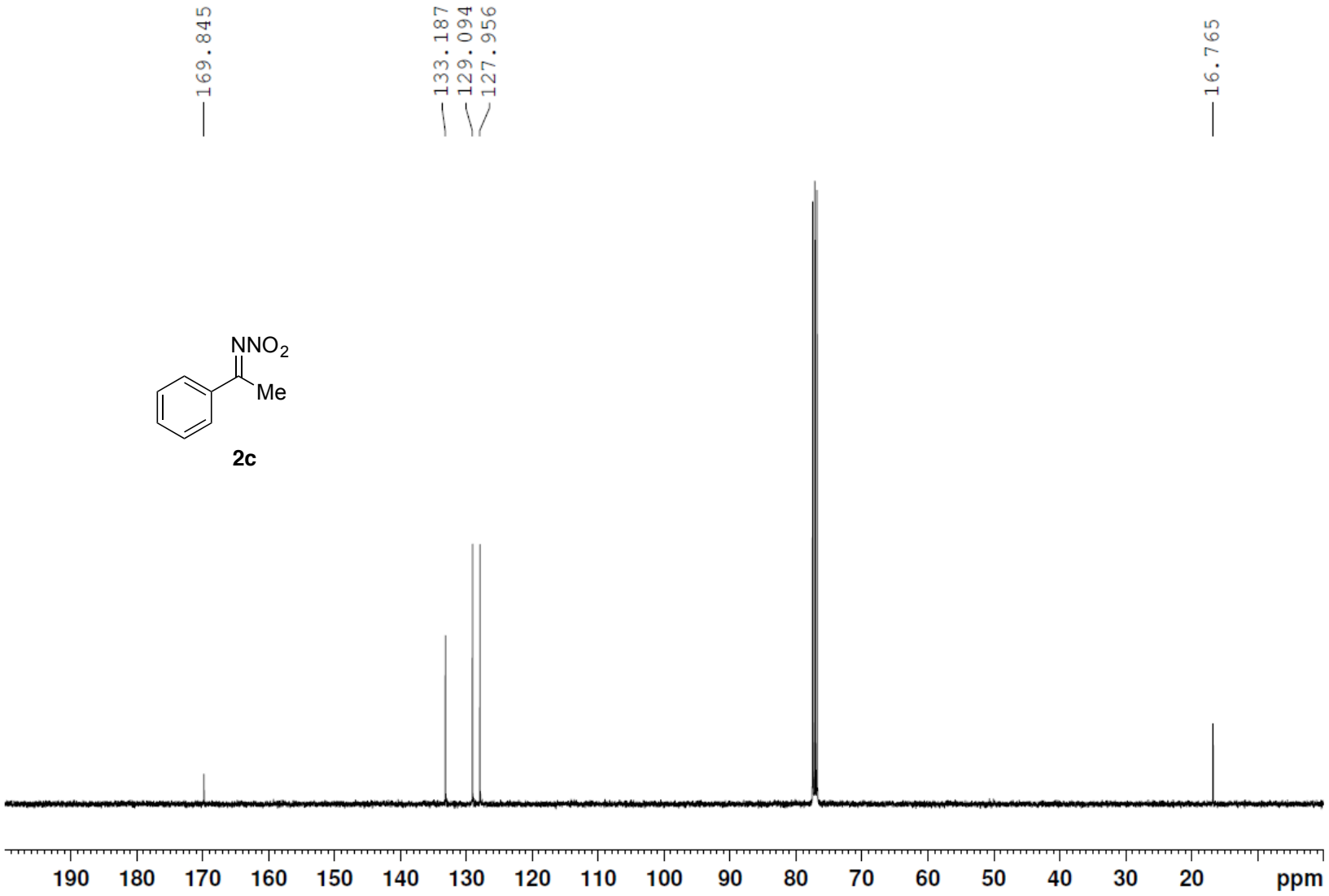
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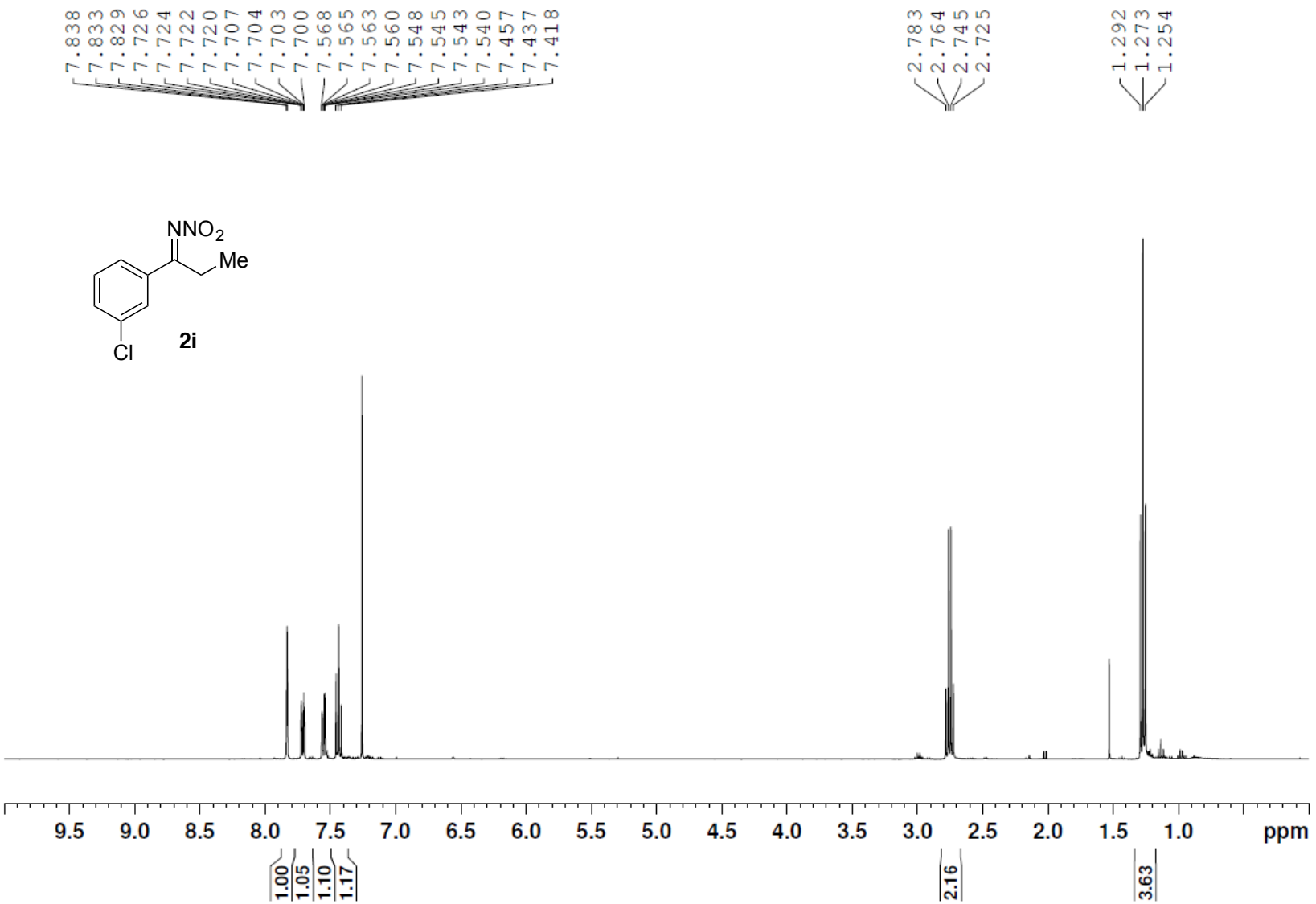
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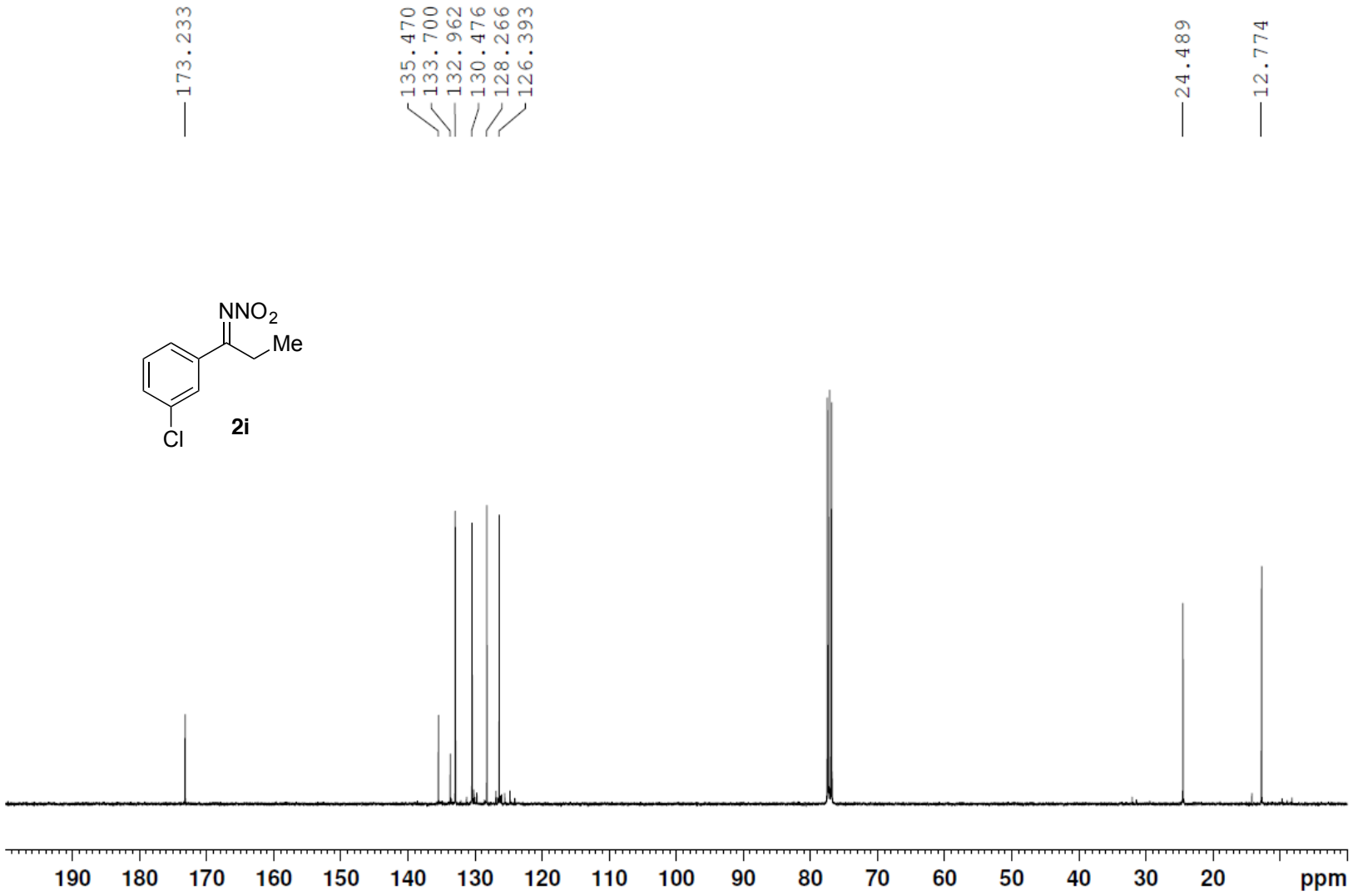
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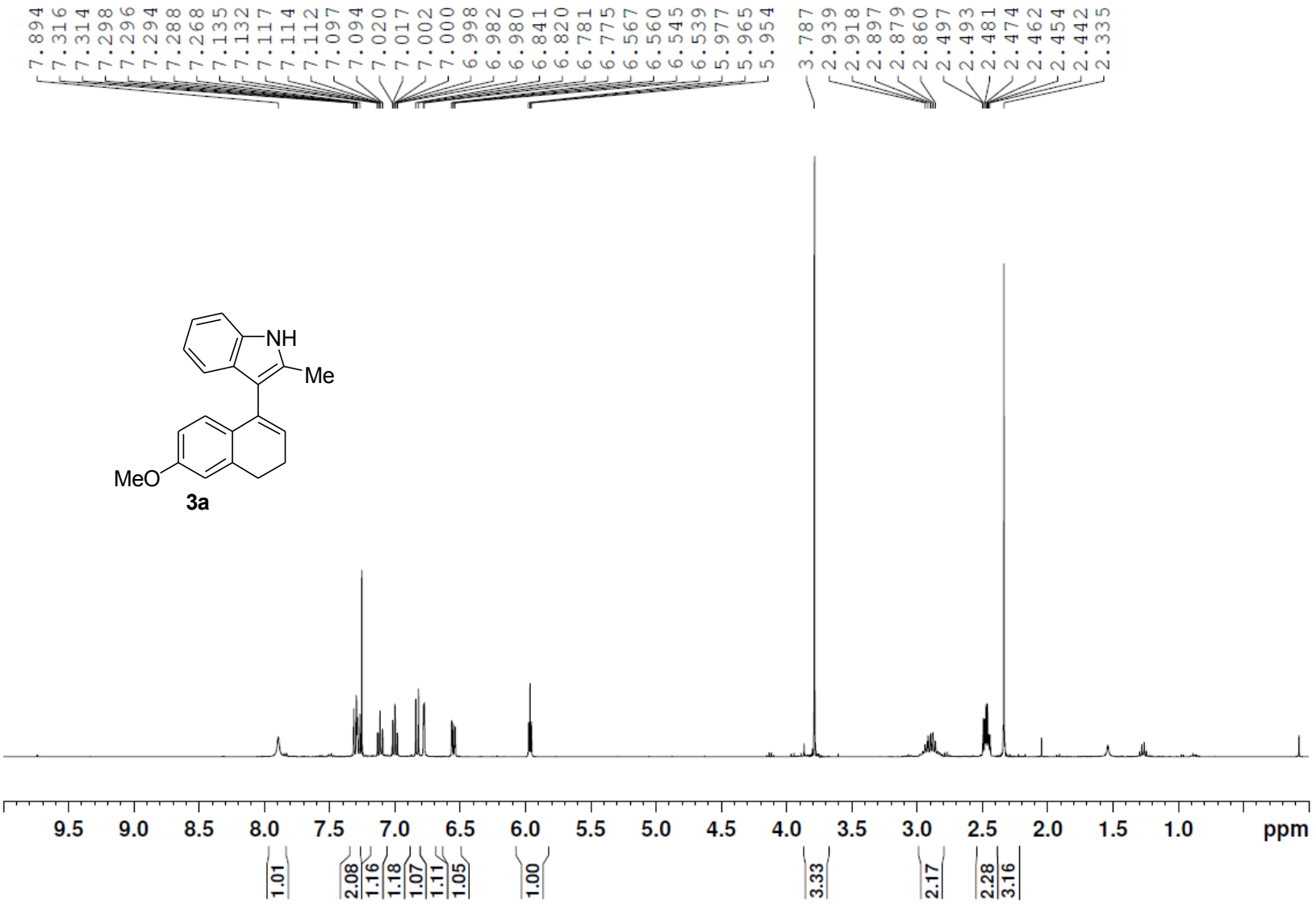
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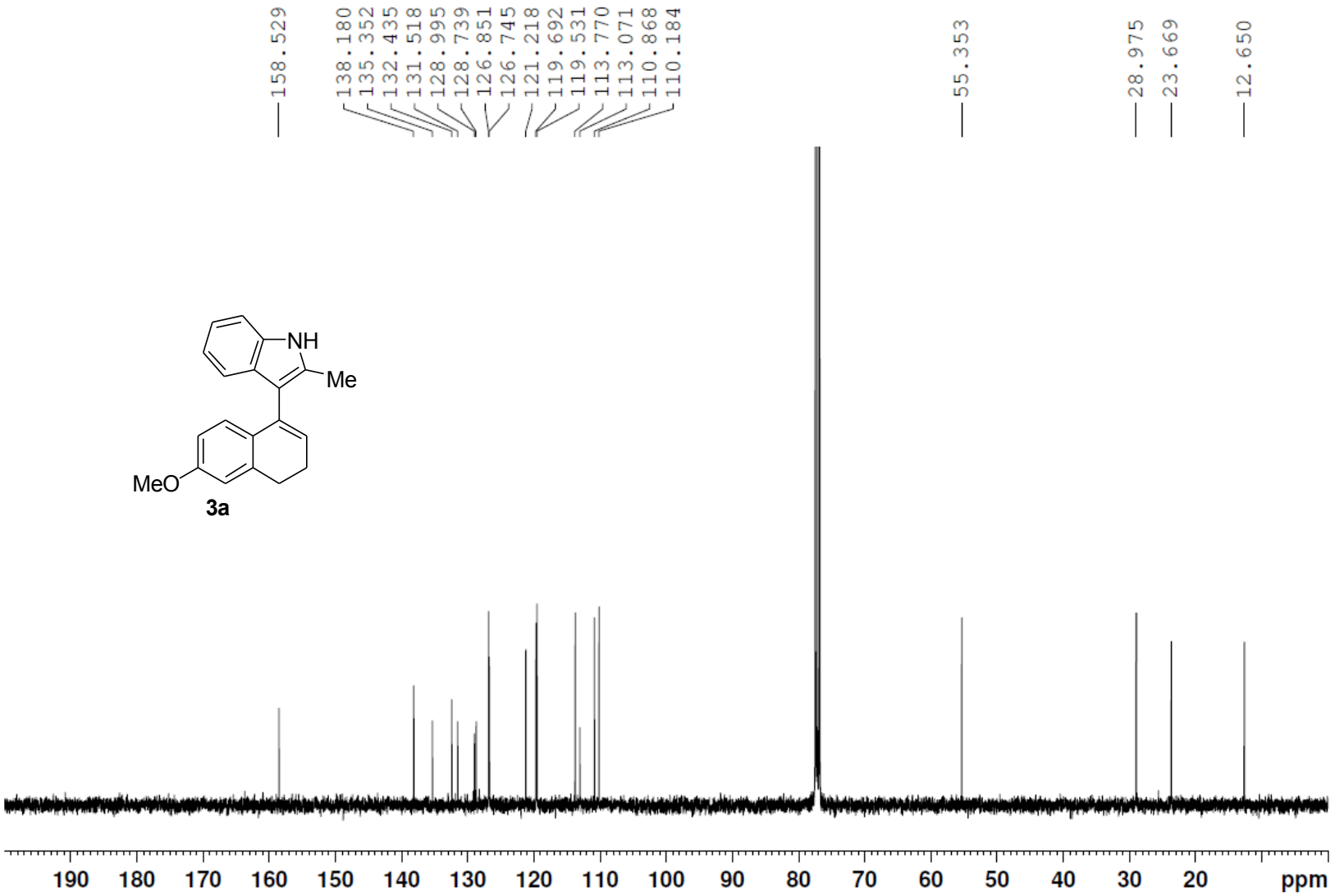
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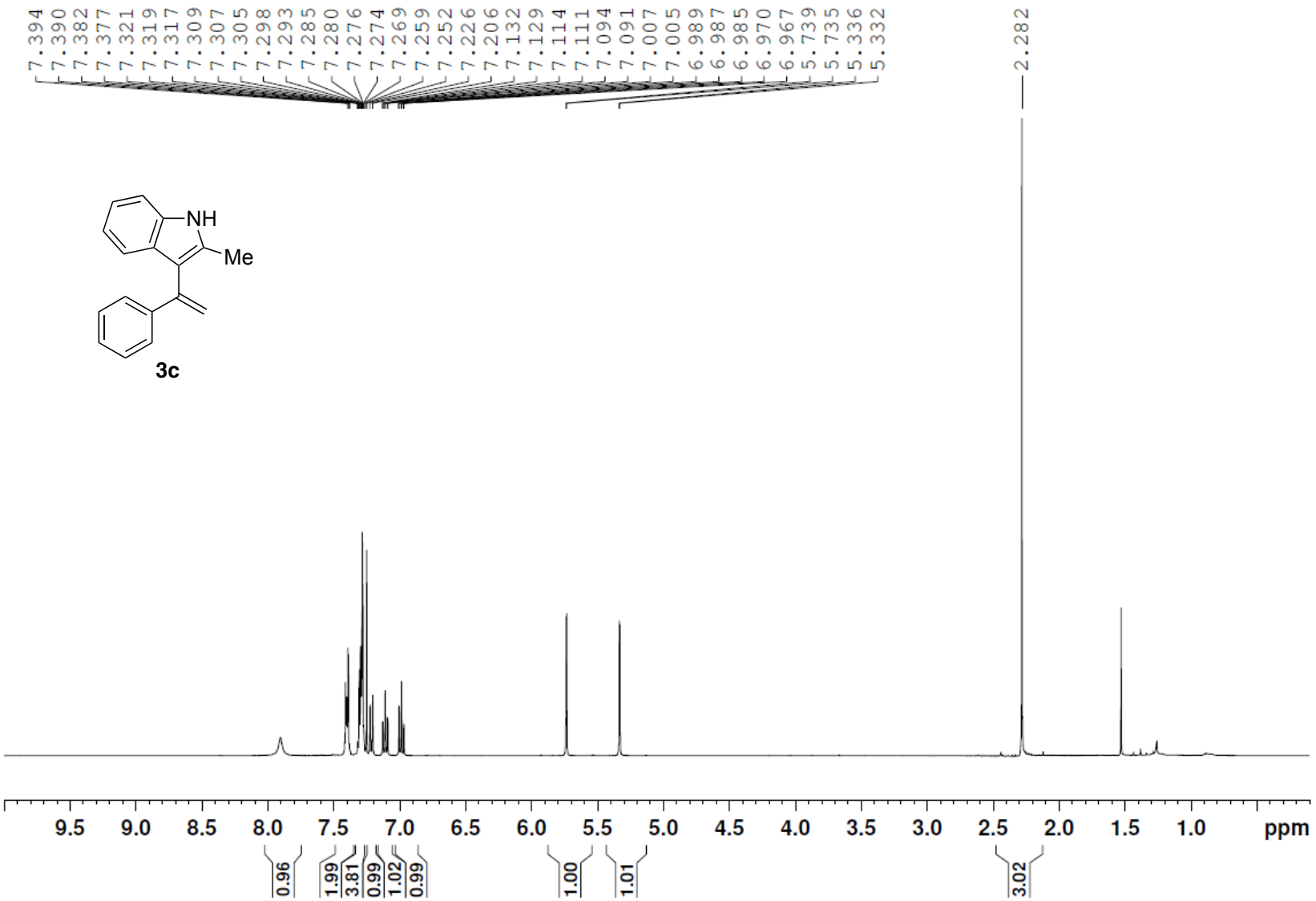
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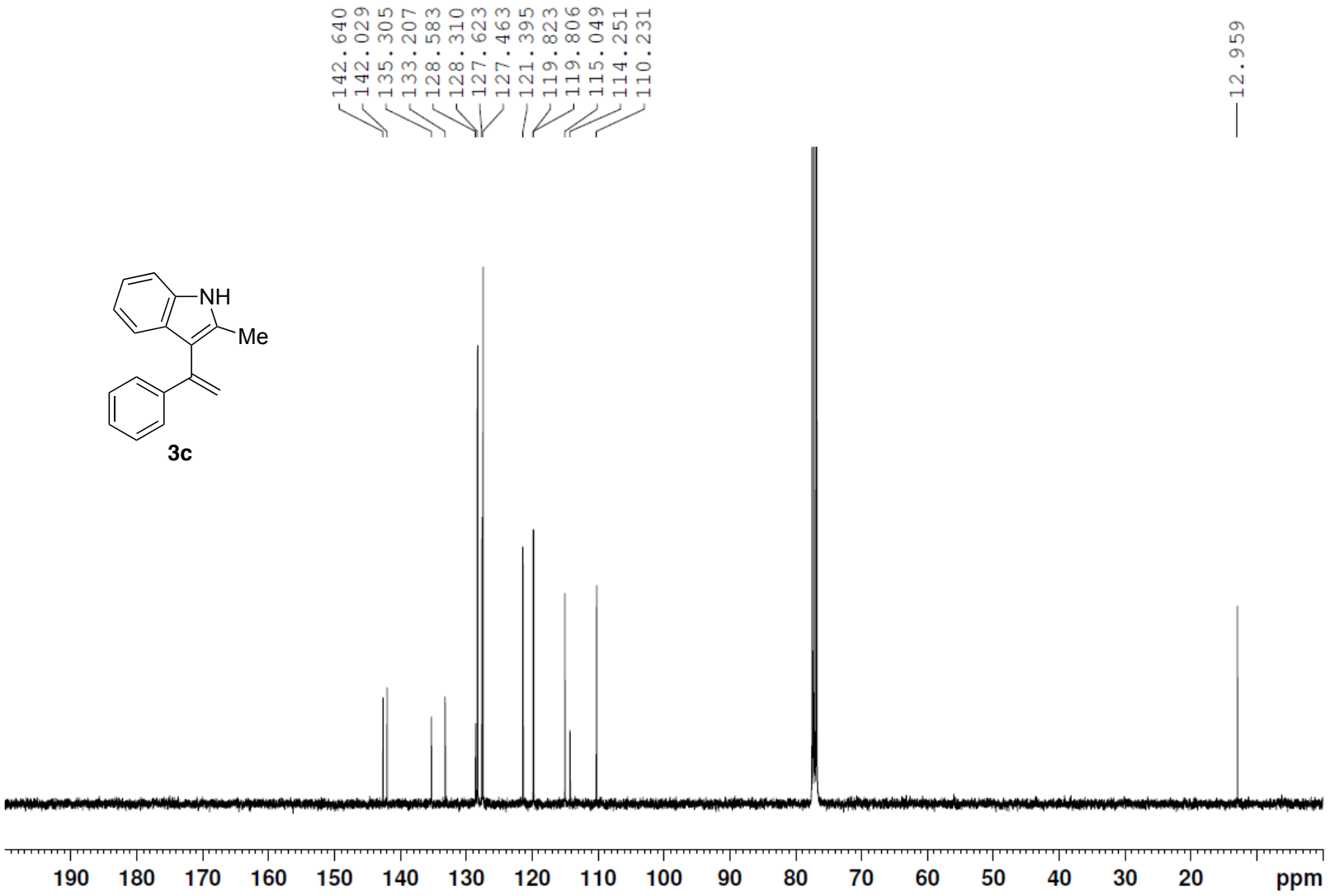
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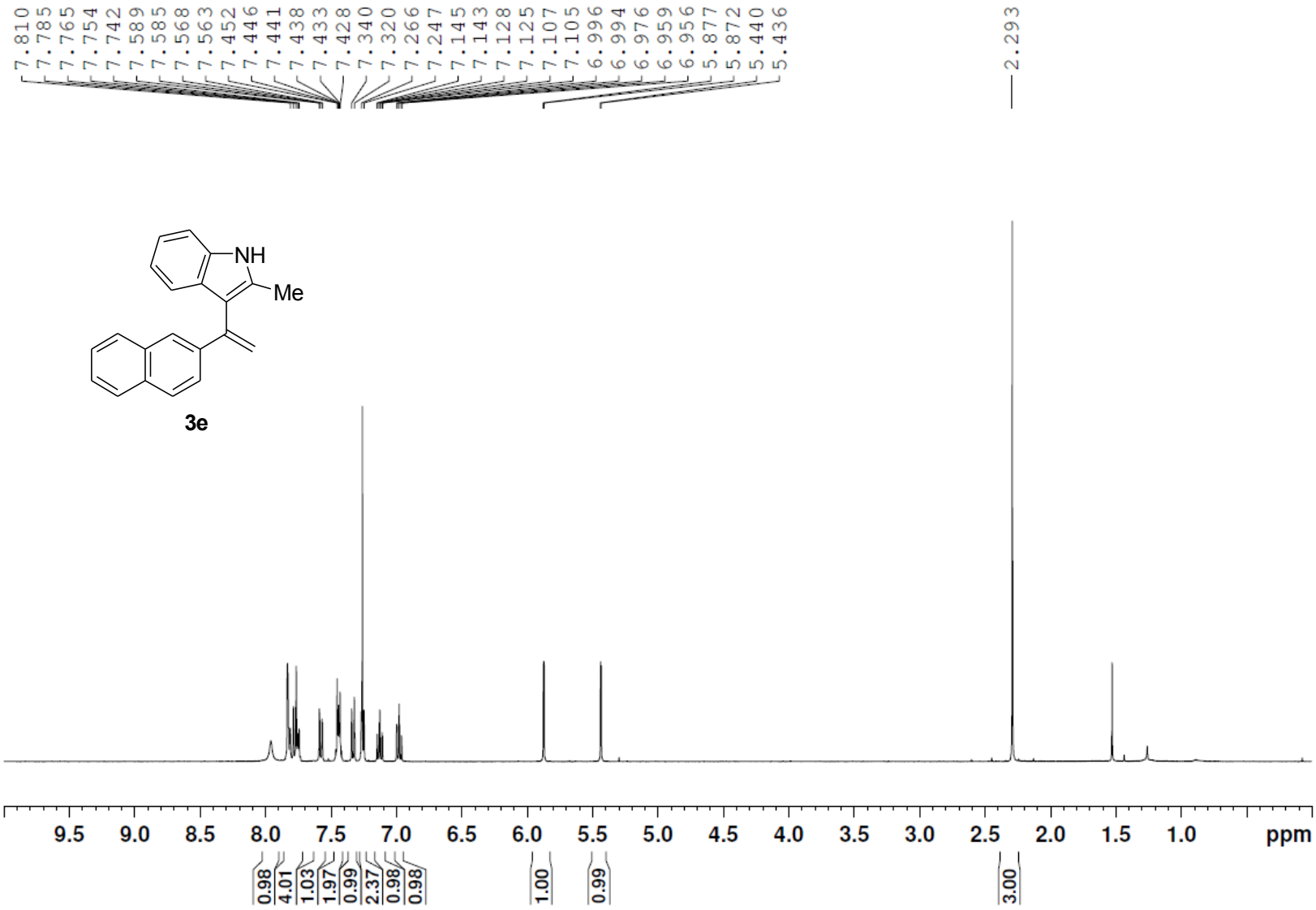
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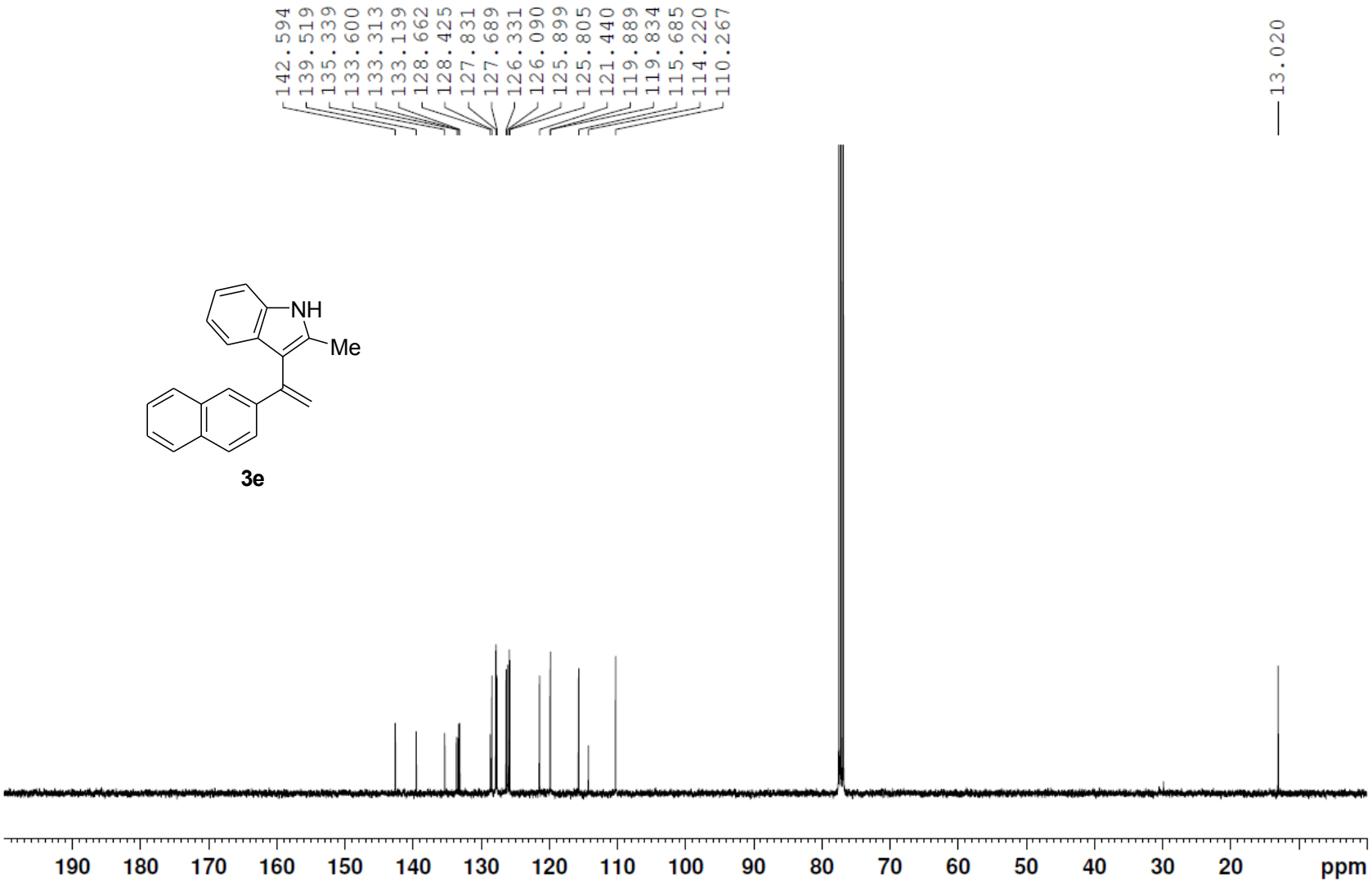
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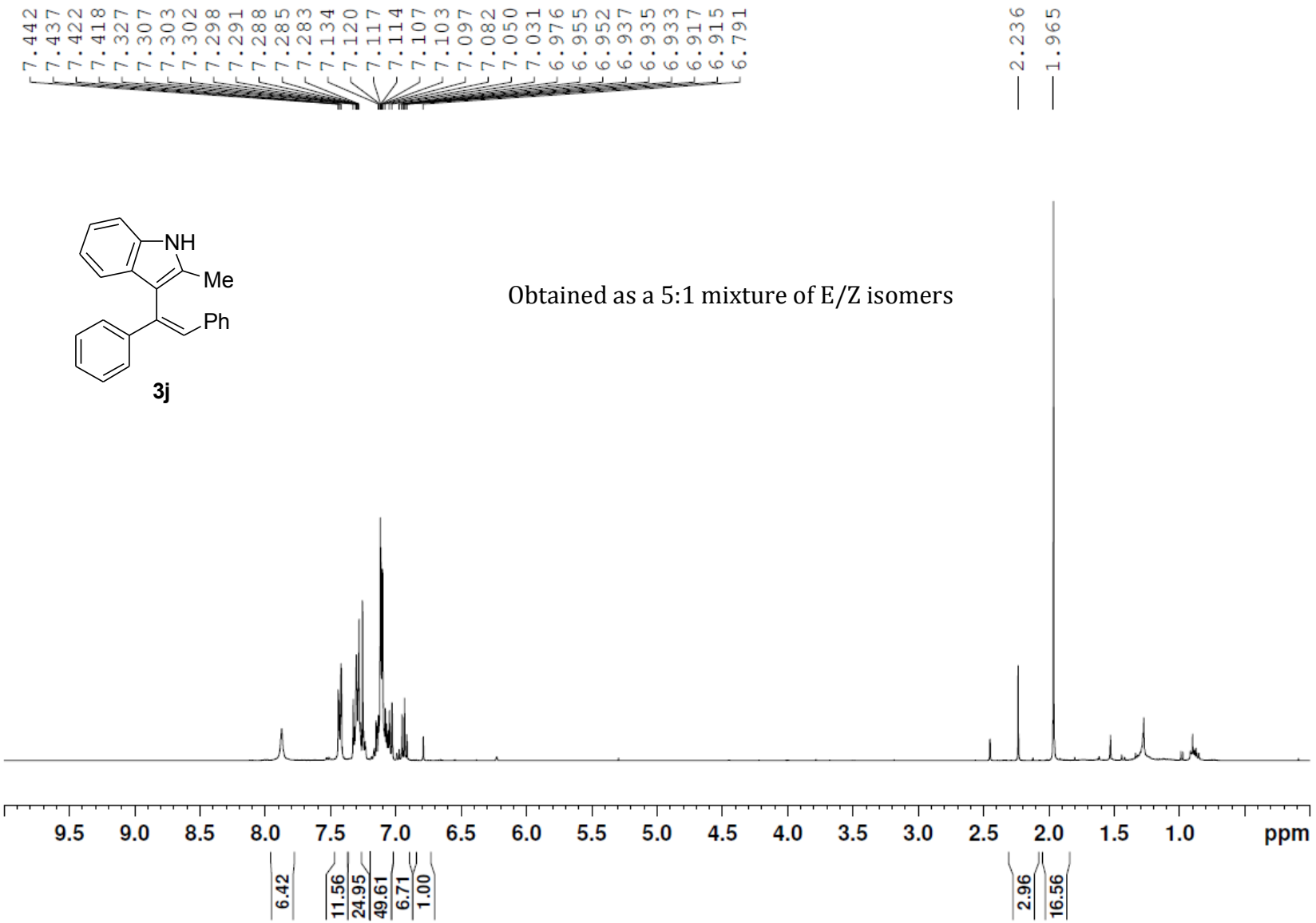
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Ph
3j
Obtained as a 5:1 mixture of E/Z isomers
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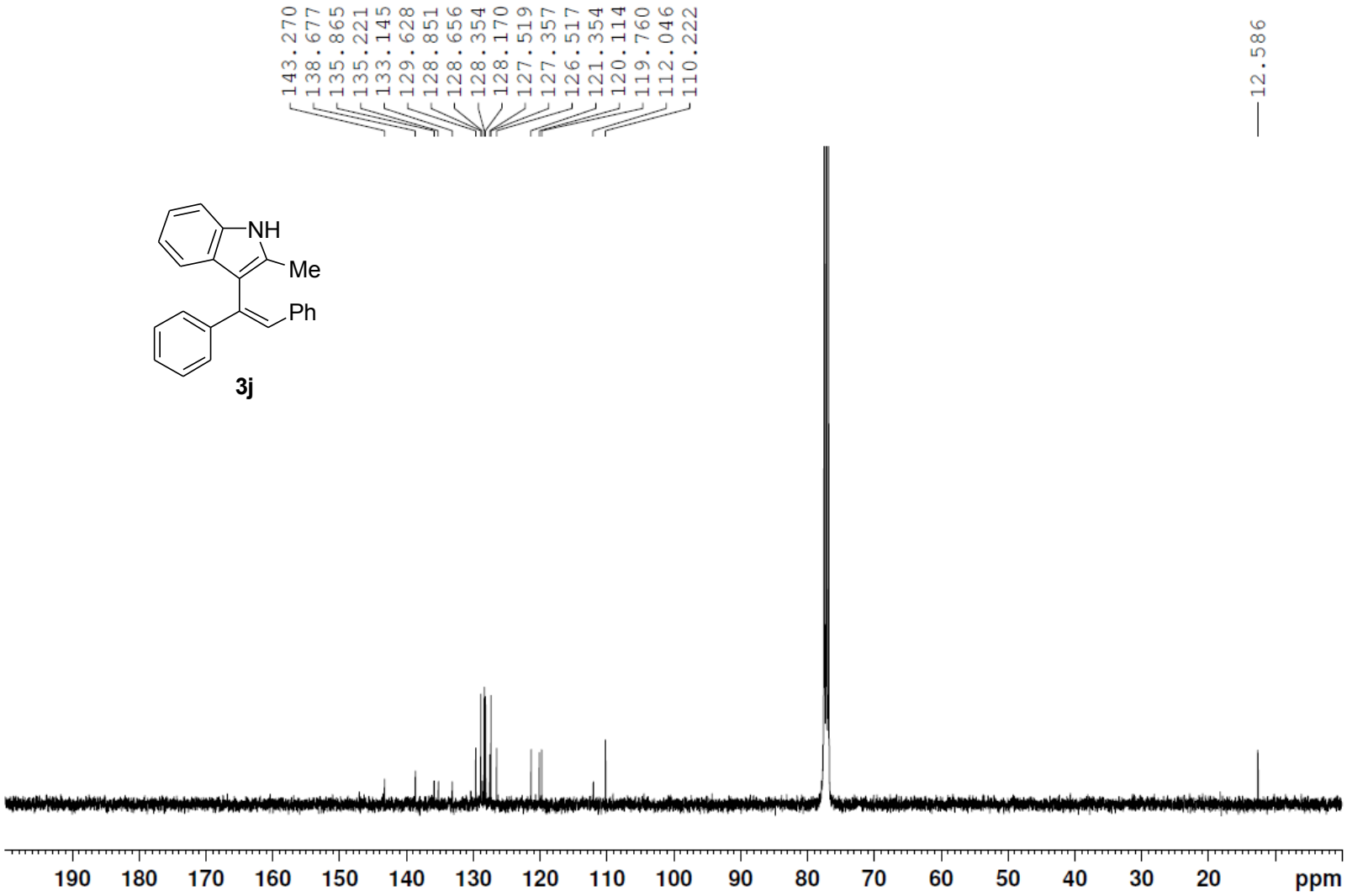
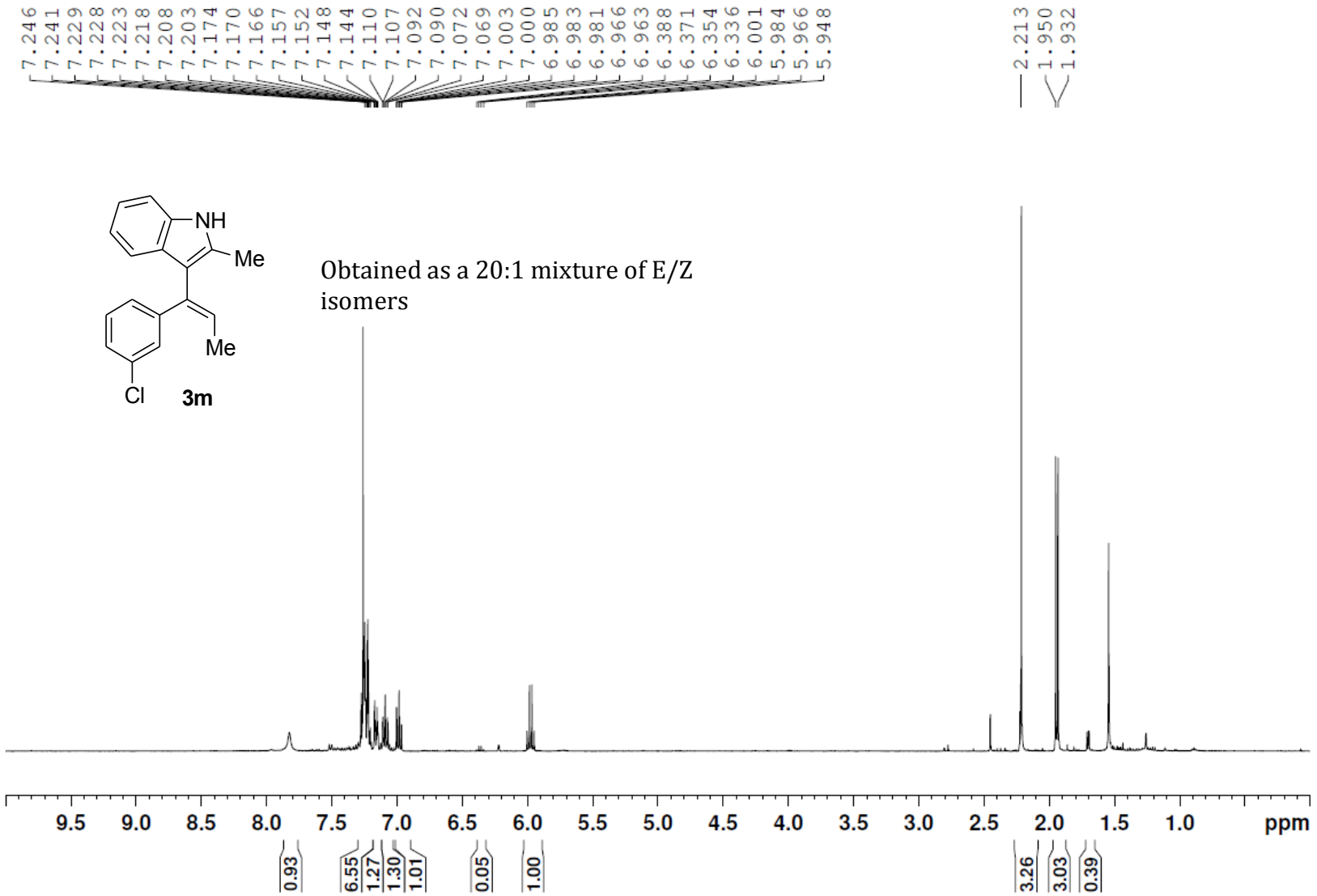
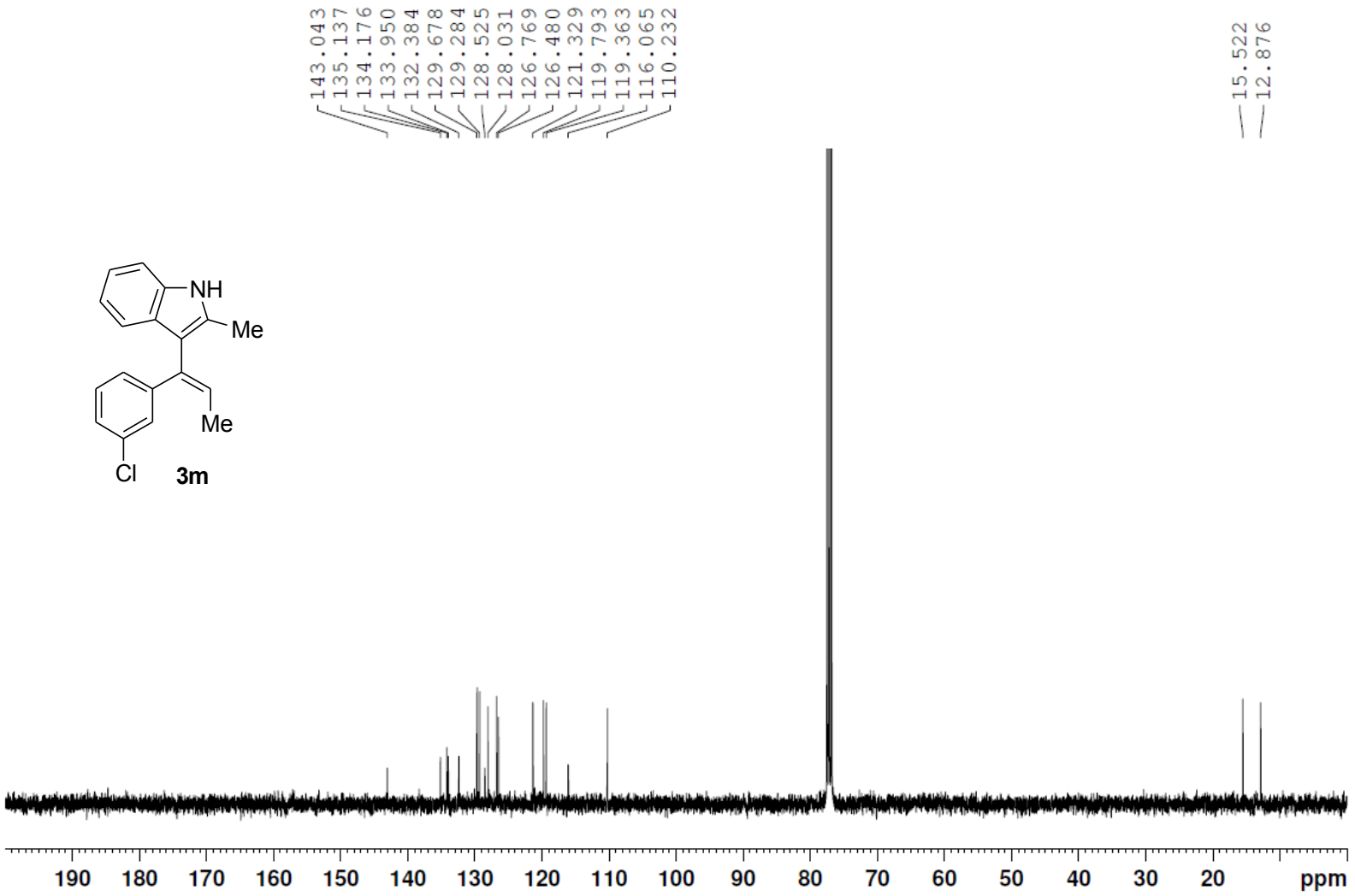
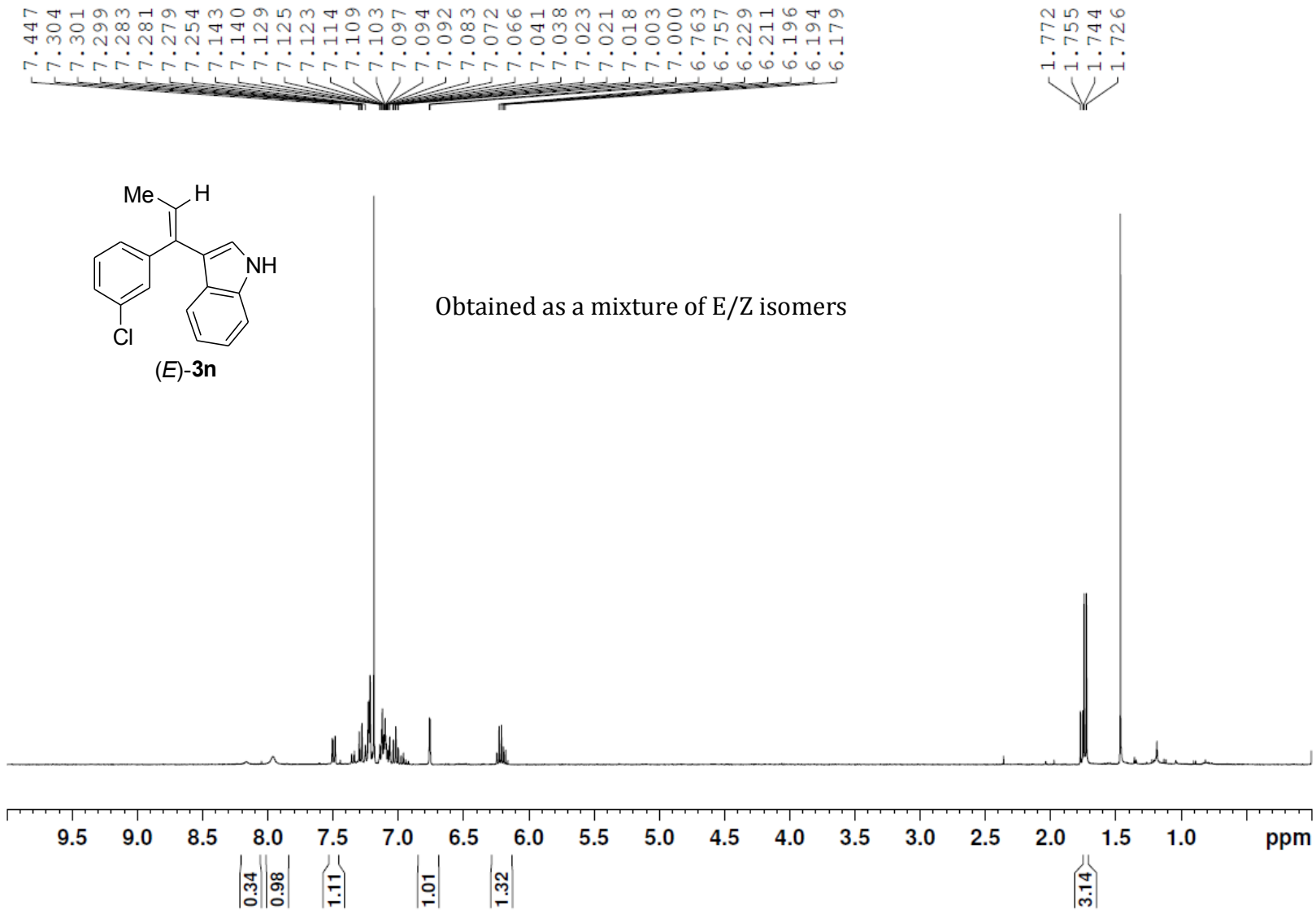
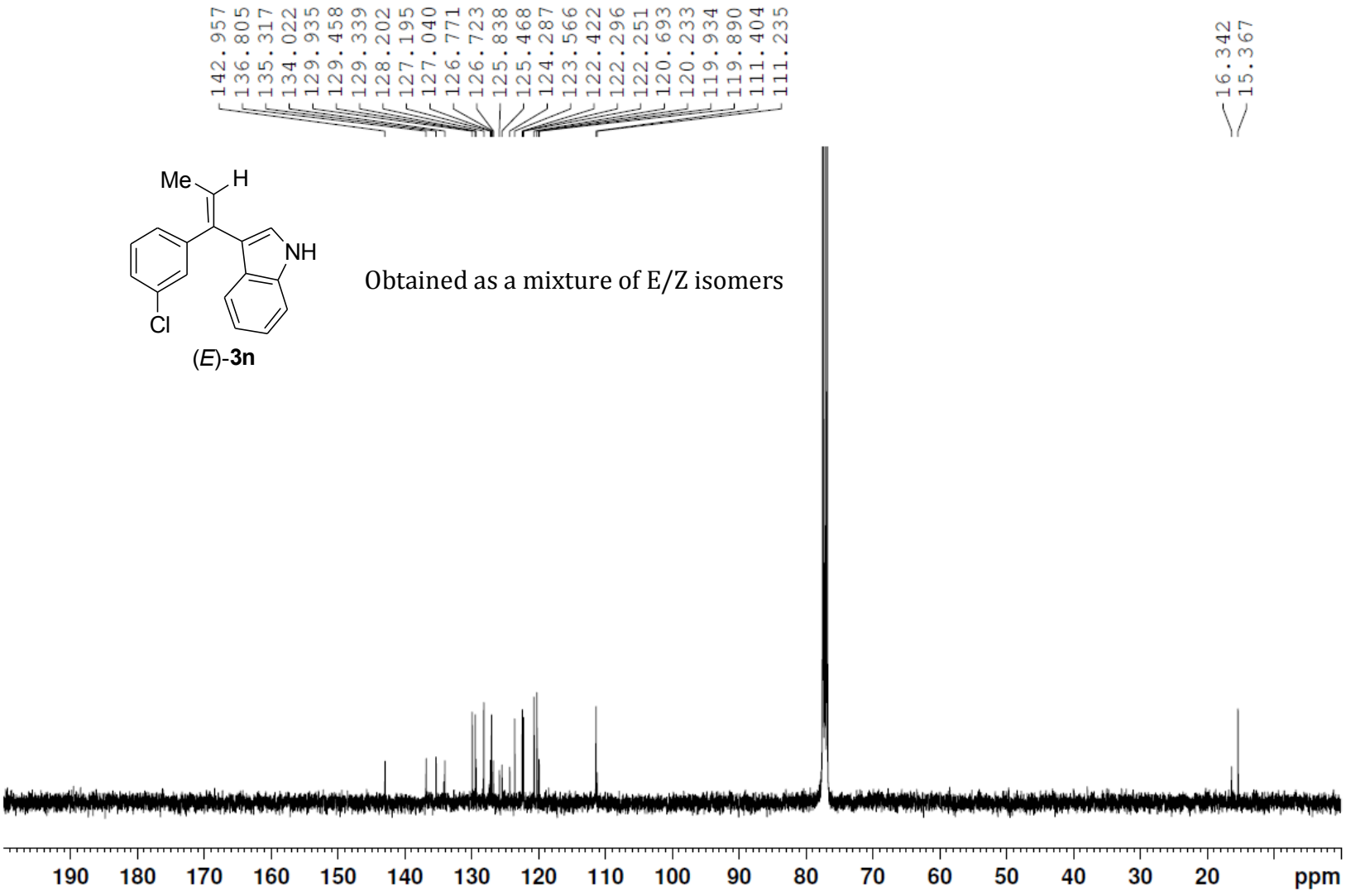
2.96
16.56


143.270
138.677
135.865
135.221
133.145
129.628
128.851
128.656
128.354
128.170
127.519
127.357
126.517
121.354
120.114
119.760
112.046
110.222
12.586
NH
Me
Ph
3j
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


7.246
7.241
7.229
7.228
7.223
7.218
7.208
7.203
7.174
7.170
7.166
7.157
7.152
7.148
7.144
7.110
7.107
7.092
7.090
7.072
7.069
7.003
7.000
6.985
6.983
6.981
6.966
6.963
6.388
6.371
6.354
6.336
6.001
5.984
5.966
5.948
2.213
1.950
1.932
NH
Me
Me
Cl
3m
Obtained as a 20:1 mixture of E/Z isomers
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.93
6.55
1.27
1.30
1.01
0.05
1.00
3.26
3.03
0.39


143.043
135.137
134.176
133.950
132.384
129.678
129.284
128.525
128.031
126.769
126.480
121.329
119.793
119.363
116.065
110.232
15.522
12.876
NH
Me
Me
Cl
3m
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

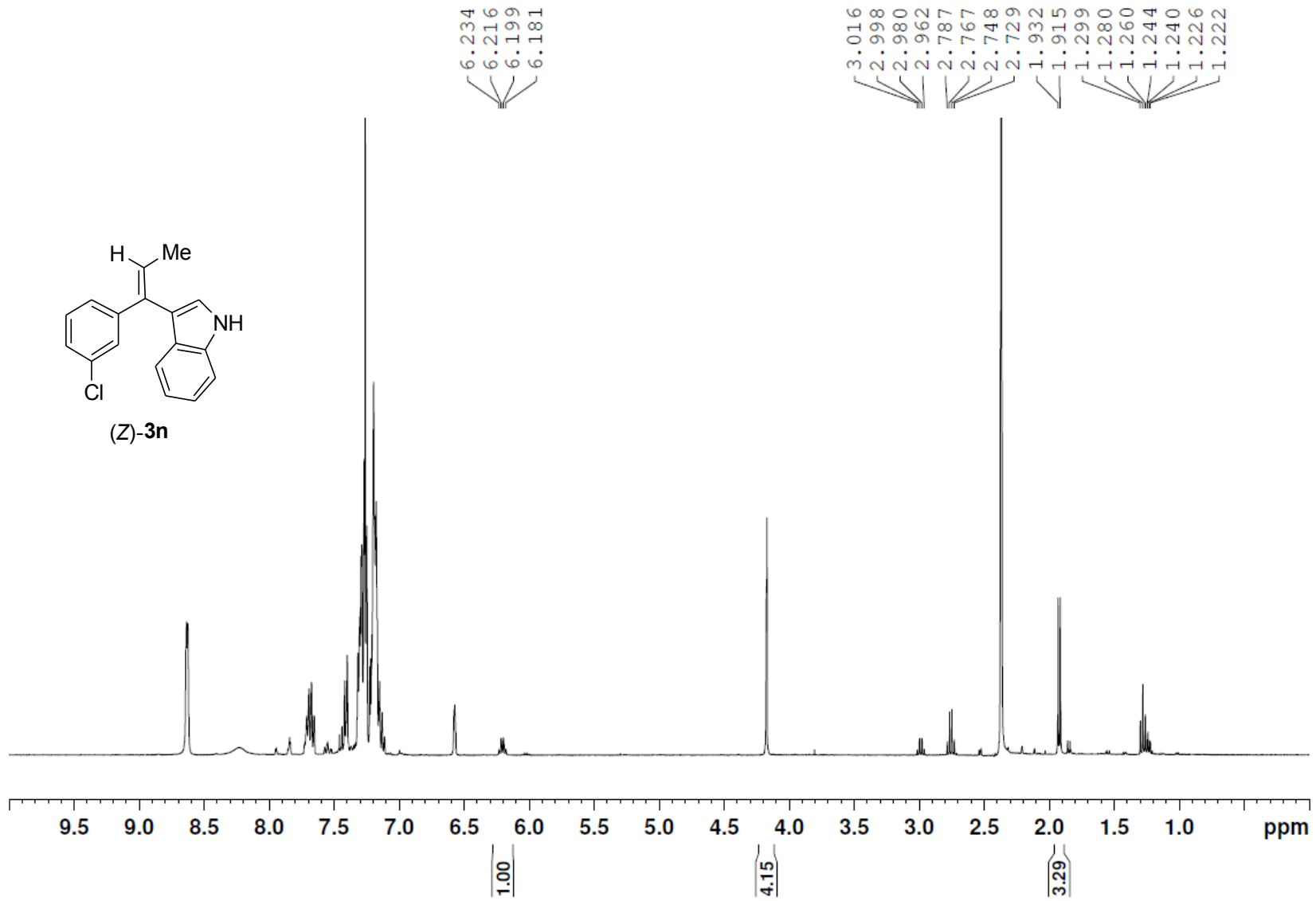

7.447
7.304
7.301
7.299
7.283
7.281
7.279
7.254
7.143
7.140
7.129
7.125
7.123
7.114
7.109
7.103
7.097
7.094
7.092
7.083
7.072
7.066
7.041
7.038
7.023
7.021
7.018
7.003
7.000
6.763
6.757
6.229
6.211
6.196
6.194
6.179
1.772
1.755
1.744
1.726
Me
H
NH
Cl
(E)-3n
Obtained as a mixture of E/Z isomers
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.34
0.98
1.11
1.01
1.32
3.14



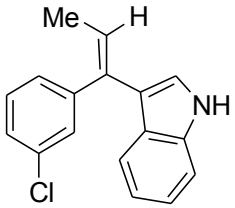
(*E*)-**3n**

Obtained as a mixture of E/Z isomers

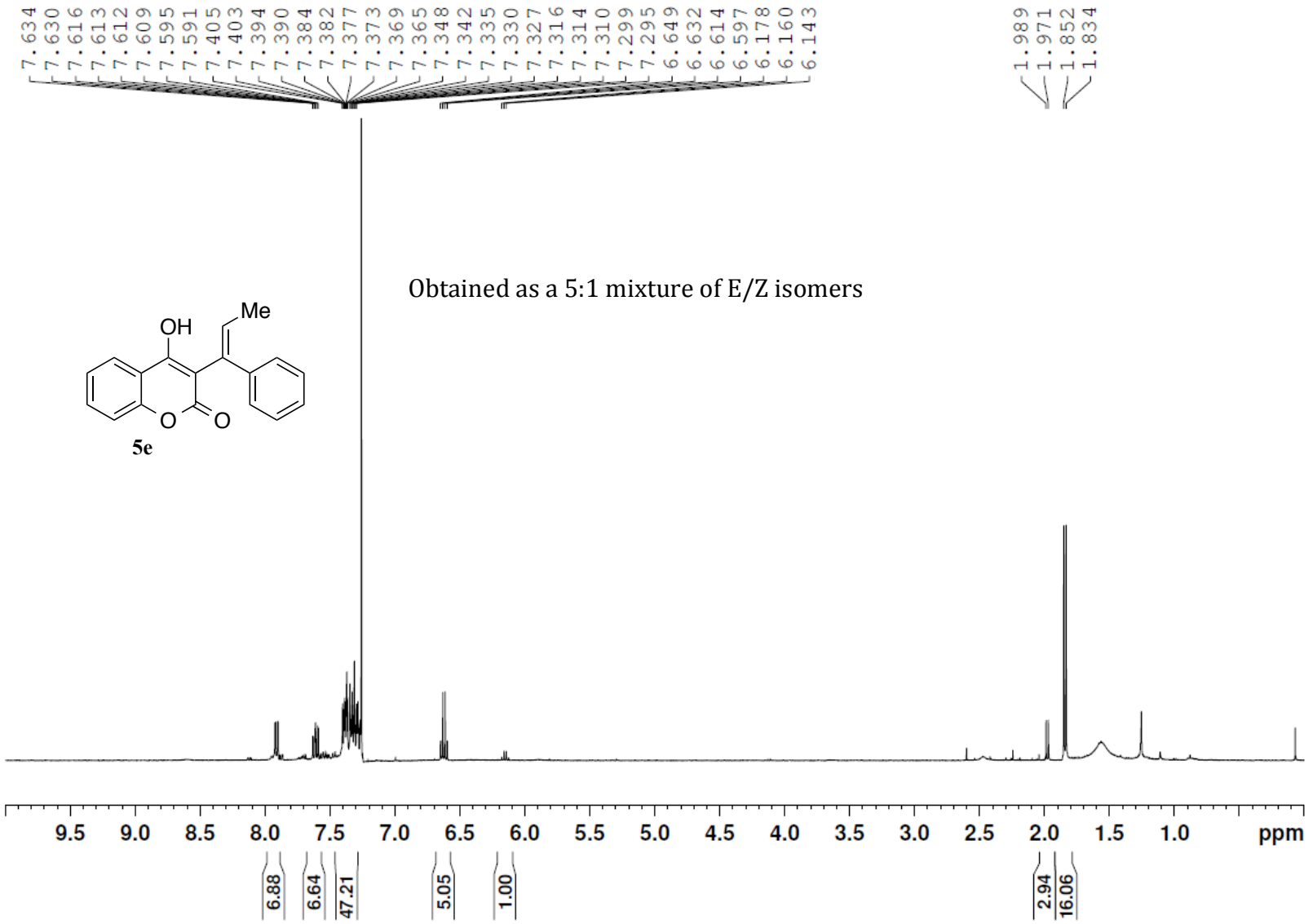
Crude ^{1}H NMR with ferrocene (4.17 ppm) as an internal standard

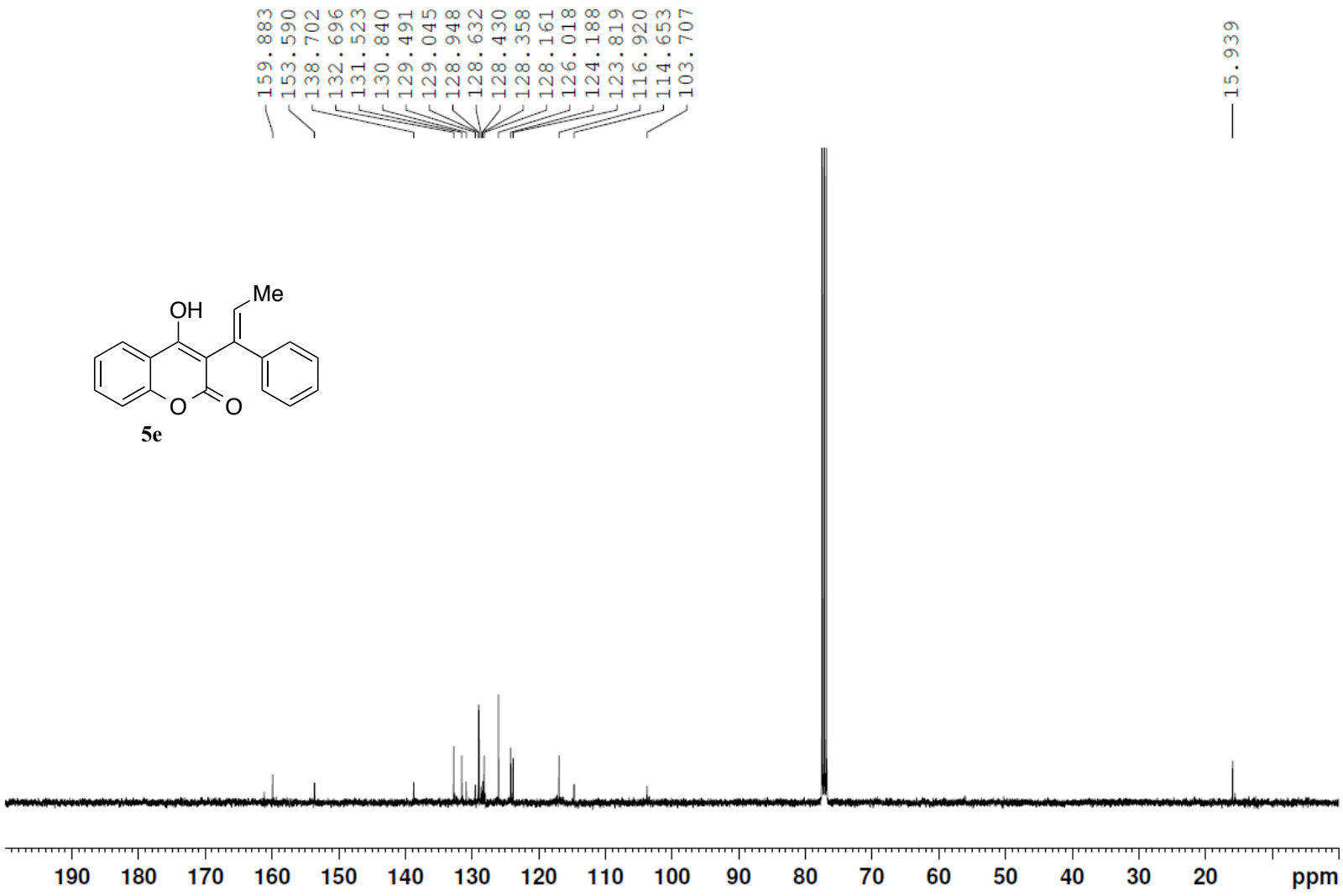


NOSEY

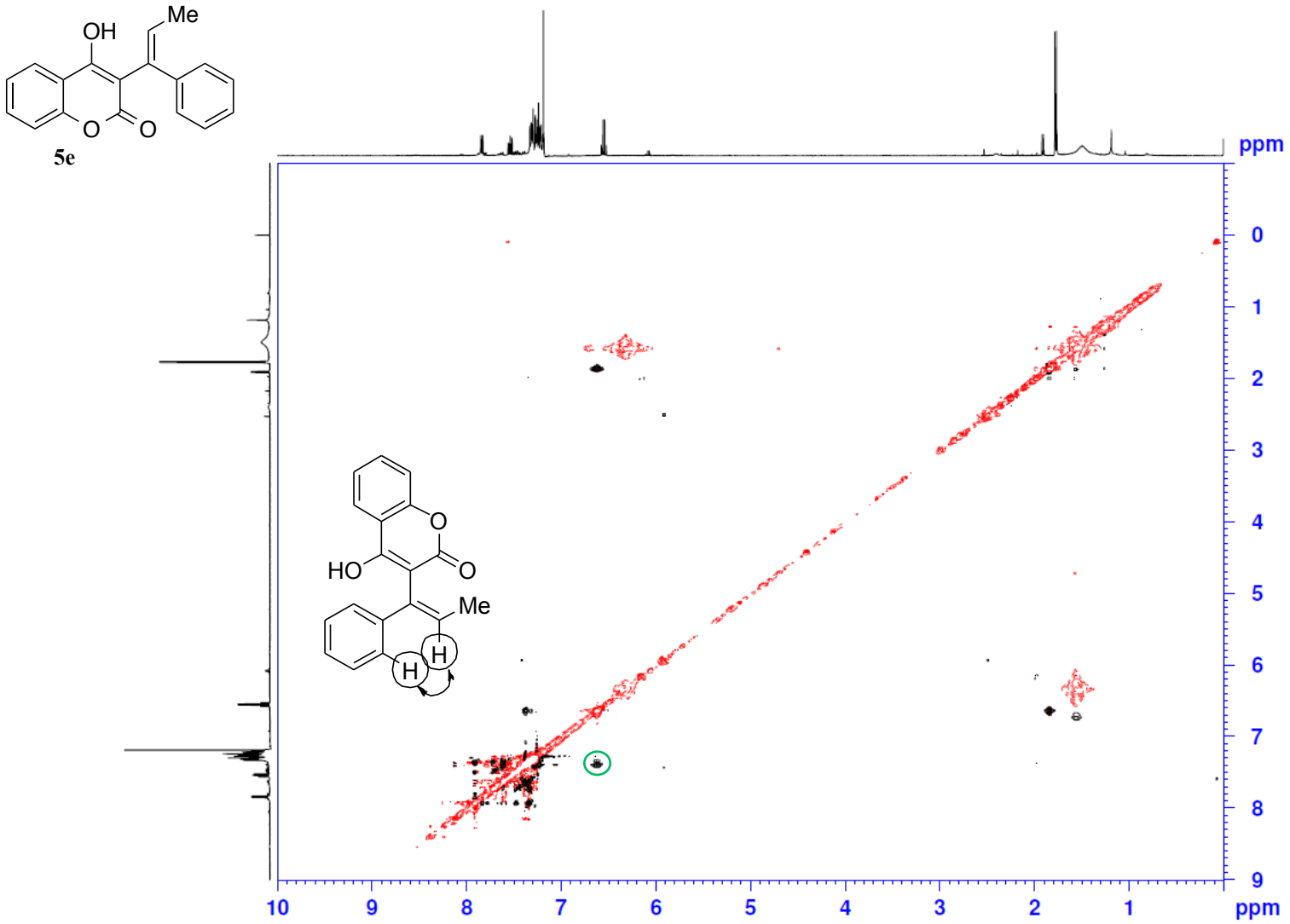


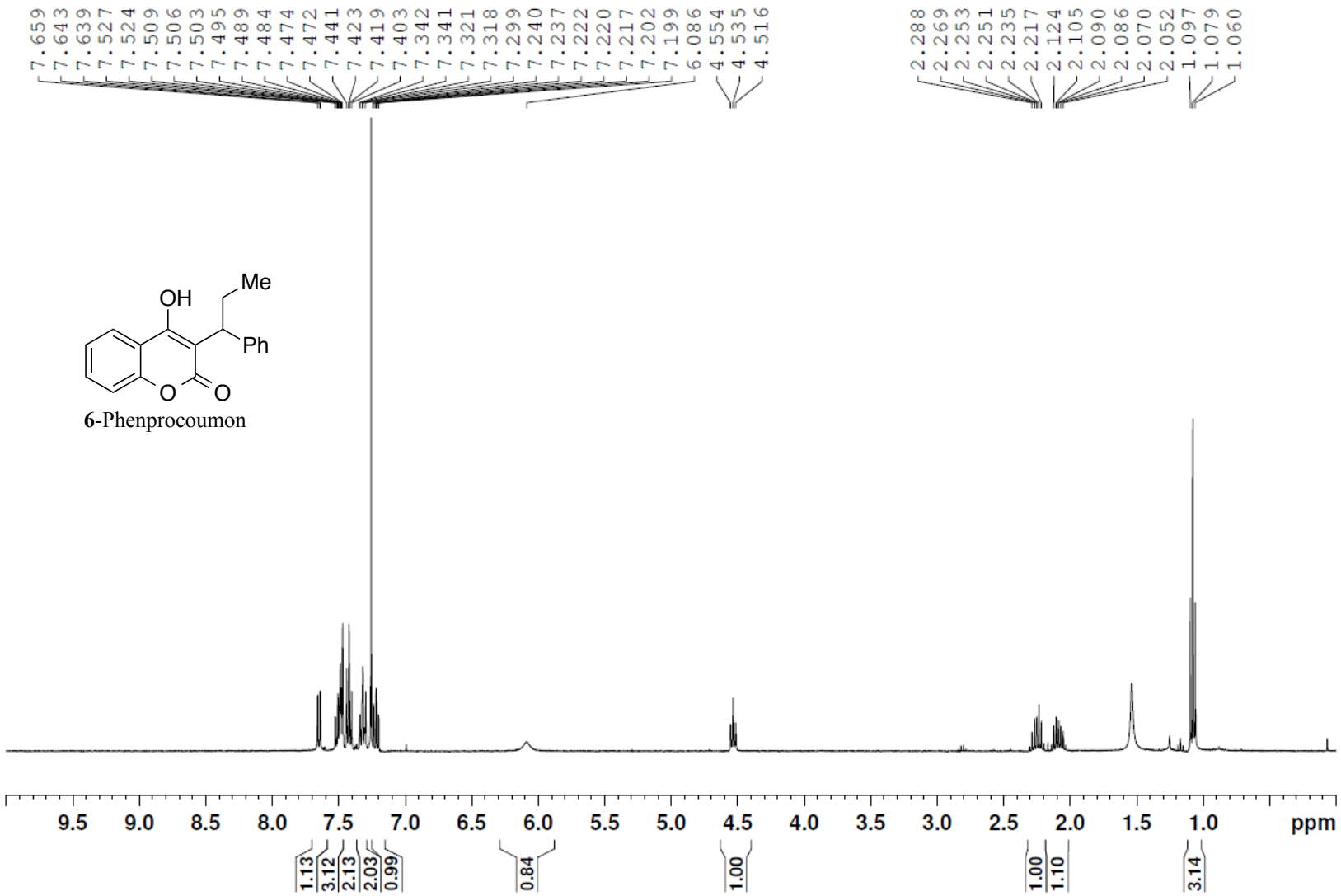
(*E*)-**3n**


7.634
7.630
7.616
7.613
7.612
7.609
7.595
7.591
7.405
7.403
7.394
7.390
7.384
7.382
7.377
7.373
7.369
7.365
7.348
7.342
7.335
7.330
7.327
7.316
7.314
7.310
7.299
7.295
6.649
6.632
6.614
6.597
6.178
6.160
6.143
1.989
1.971
1.852
1.834
Obtained as a 5:1 mixture of E/Z isomers
OH
Me
O
O
5e
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
6.88
6.64
47.21
5.05
1.00
2.94
16.06

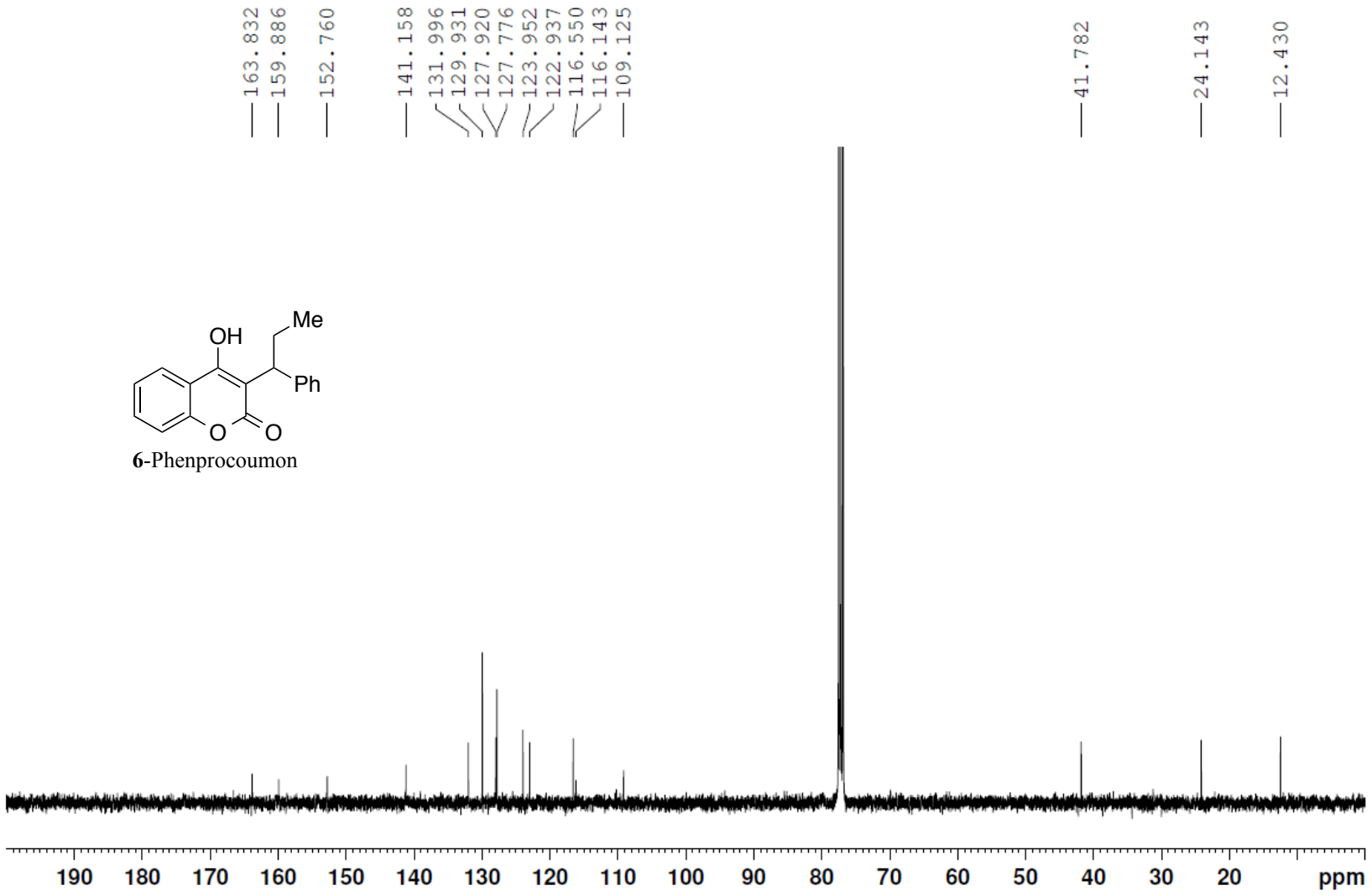

159.883
153.590
138.702
132.696
131.523
130.840
129.491
129.045
128.948
128.632
128.430
128.358
128.161
126.018
124.188
123.819
116.920
114.653
103.707
15.939
OH
Me
O
O
5e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

NOESY





6-Phenprocoumon



6-Phenprocoumon